Bleeding disorders

Sven Olson and Riten Kumar

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The online version of this chapter contains an educational multimedia component on coagulation of blood.

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Off-label drug use: Sven Olson and Riten Kumar: rFVIIa for management of bleeding in hemophilia at doses and regimens that are not approved and for other off-label indications; antifibrinolytics for bleeding of unknown cause; prothrombin complex concentrates for treatment of factor II and X deficiency.

Overview of hemostasis

Hemostasis is the process through which bleeding is controlled at a site of damaged vascular endothelium and represents a dynamic interplay between the subendothelium, endothelium, circulating cells, and plasma proteins. The hemostatic process is often divided into 3 phases: vascular, platelet, and plasma. Although it is helpful to divide coagulation into these phases for didactic purposes, in vivo they are intimately linked and occur in a continuum. The *vascular phase* is mediated by the release of locally active vasoactive agents that result in vasoconstriction at the site of injury and reduced blood flow. Vascular injury exposes the underlying subendothelium and procoagulant proteins, including von Willebrand factor (VWF), collagen, and tissue factor (TF), which then come into contact with blood. During the *platelet phase*, platelets bind to VWF incorporated into the subendothelial matrix through their expression of glycoprotein 1b-alpha (GP1b-alpha). Platelets bound to VWF form a layer across the exposed subendothelium, a process termed *platelet adhesion*, and subsequently are *activated* via receptors, such as the collagen receptors integrin $\alpha_2\beta_1$ and glycoprotein (GPVI), resulting in calcium mobilization, granule release, activation of the fibrinogen receptor integrin $\alpha_{IIb}\beta_3$, and subsequent *platelet aggregation* (Figure 10-1). For a more detailed discussion of platelet function, please see Chapter 11.

The *plasma phase* of coagulation can be further subdivided into initiation, priming, and propagation (Figure 10-2; see video in online edition). Initiation begins when vascular injury also leads to exposure of TF in the subendothelium and on damaged endothelial cells. TF binds to the small amounts of circulating activated factor VII (FVIIa), resulting in formation of the TF:FVIIa complex, also known as the extrinsic tenase complex; this complex binds to and activates factor X (FX) to activated FX (FXa). FXa forms a complex with activated factor V (FVa), released from collagen-bound platelets, to convert a small amount of prothrombin to thrombin. The small amount of thrombin generated at this stage is able to initiate coagulation and generate an amplification loop by cleaving factor VIII (FVIII) from VWF, activating FVIII, FXI, and platelets, which result in exposure of membrane phospholipids and further release of partially activated FV. At the end of the initiation and priming phases, the platelet is primed with an exposed phospholipid surface with bound activated cofactors (FVa and FVIIIa). During the propagation phase, activated factor IX (FIXa), generated either by the

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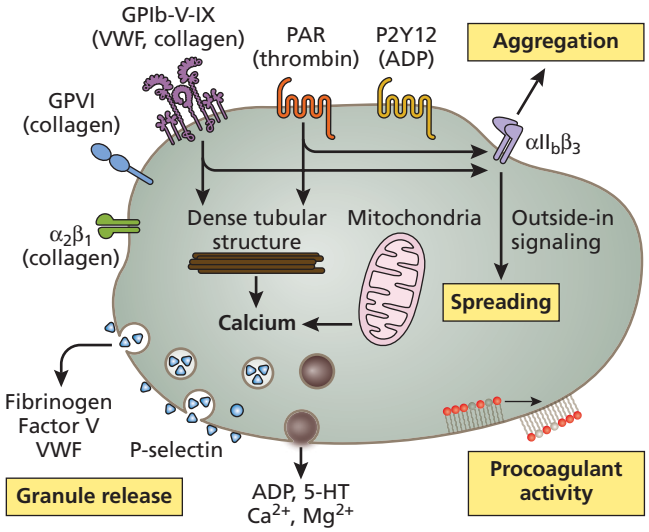

Figure 10-1 Platelet activation. Platelets can undergo activation through stimulation by soluble agonists, such as thrombin, or by contact (adherence) to the subendothelial matrix. This simplified cartoon shows several platelet components, including receptors and granules as well as the pathways of activation and the effect on platelet responses, such as aggregation, spreading, granule release, and procoagulant activity. 5-HT, 5-hydroxytryptamine.

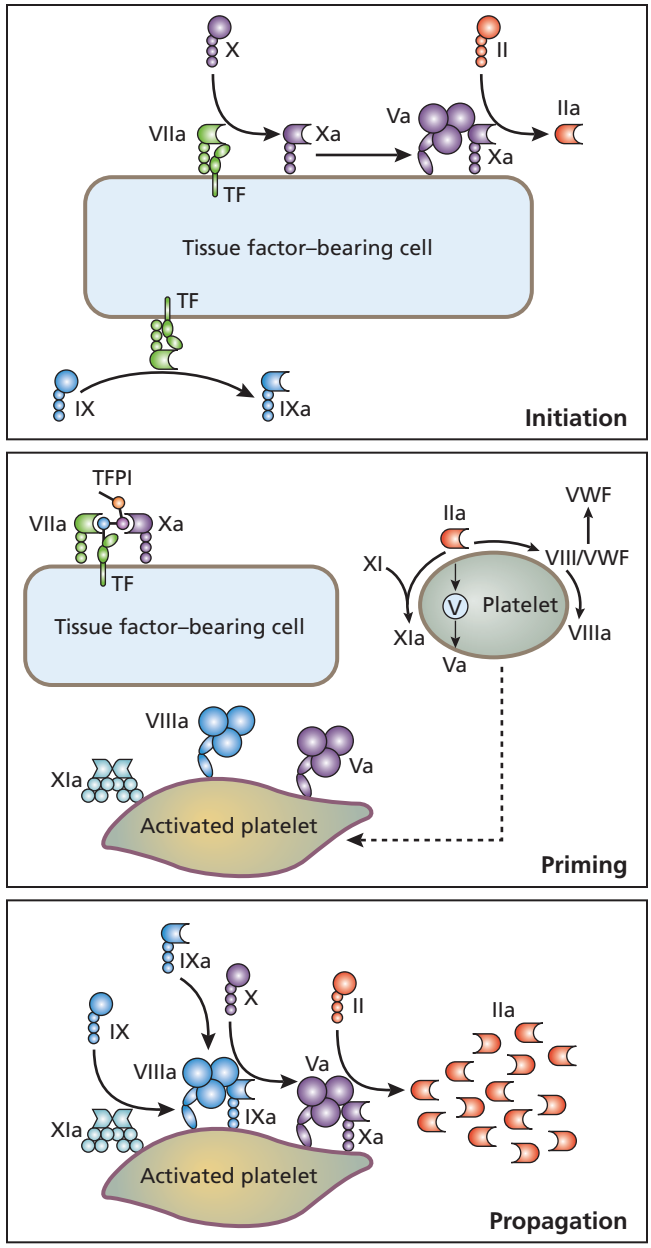

Figure 10-2 Thrombin generation occurs on 2 distinct cellular surfaces. The first is the tissue factor (TF)–bearing cell at the site of vascular injury. *Initiation* of coagulation occurs on the TF-bearing cell through generation of a small amount of thrombin that then goes on to *prime* the system by activating platelets, releasing FVIII from VWF and activating it, and activating factor XI. At the end of the priming step, the activated platelet with bound FXIa and cofactors FVa and FVIIIa are ready to form essential complexes, tenase (FVIIIa:FIXa) and prothrombinase (FVa:FXa) and through an amplification loop can *propagate* thrombin generation, forming a burst of thrombin capable to form a hemostatic fibrin clot.

action of FXIa on the platelet surface or TF-VIIa complex on the TF-bearing cell, binds to its cofactor FVIIIa to form the potent intrinsic tenase complex. FX is then bound and cleaved by the tenase complex (FIXa:FVIIIa), leading to large amounts of FXa, which in association with its cofactor FVa, forms the prothrombinase complex on the activated platelet surface. The prothrombinase complex (FXa:FVa) then binds and cleaves prothrombin leading to an ultimate burst of thrombin sufficient to convert fibrinogen to fibrin (Figure 10-3) and result in subsequent clot formation. The formed clot is stabilized by the thrombin-mediated activation of factor XIII (FXIII), which acts to cross-link fibrin, and thrombin-activatable fibrinolysis inhibitor (TAFI), which acts to remove lysine residues from the fibrin clot, thereby limiting plasmin binding. Ultimately, the clot undergoes fibrinolysis, resulting in the restoration of normal blood vessel architecture. The fibrinolytic process is initiated by the release of tissue plasminogen activator (tPA) near the site of injury. tPA converts plasminogen to plasmin, which (via interactions with lysine and arginine residues on fibrin) cleaves the fibrin into dissolvable fragments, called fibrin split products.

Both the hemostatic and fibrinolytic processes are regulated by inhibitors that limit coagulation at the site of injury and quench the reactions, thereby preventing systemic activation and pathologic propagation of coagulation. The hemostatic system has 3 main inhibitory pathways; antithrombin (AT), the protein C:protein S complex, and tissue factor pathway inhibitor (TFPI).

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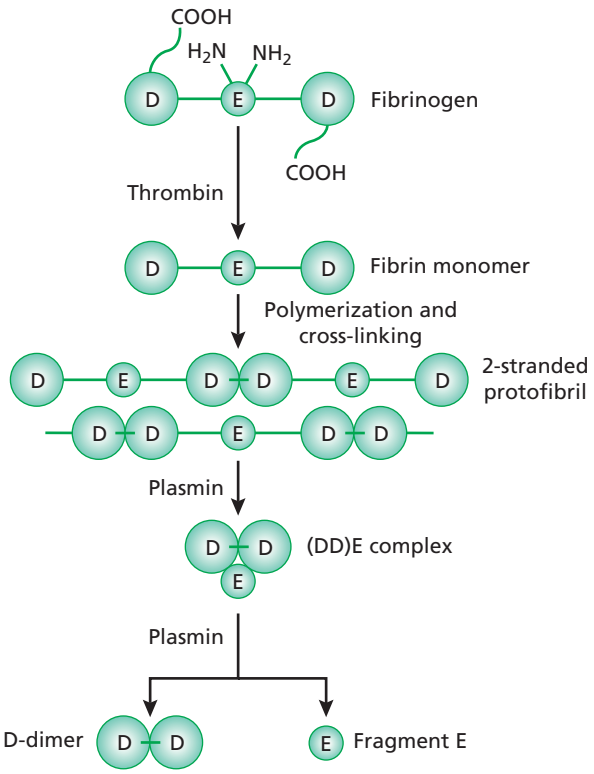

Figure 10-3 Fibrin formation and degradation. Fibrinogen has a trinocular structure with a central E and 2 D domains. Thrombin cleaves fibrinopeptides A and B (not depicted), located in the E domain. The resultant fibrin monomers polymerize nonenzymatically forming fibrin polymers. Factor XIIIa cross-links the D domains of nearby fibrin monomers. Plasmin degrades cross-linked fibrin, thereby generating (DD)E complexes composed of an E fragment noncovalently bound to D-dimer. With further plasmin attack, the (DD) E complex is degraded into fragment E and D-dimer.

AT released at the margins of endothelial injury binds in a 1:1 complex with thrombin, inactivating thrombin not bound by the developing clot. AT also rapidly inactivates FXa; thus, any excess FXa generated by the TF:FVIIa complex during initiation is inactivated and unable to migrate to the activated platelet surface. Excess free thrombin at the clot margins binds to thrombomodulin, a receptor expressed on the surface of intact endothelial cells that, when complexed with thrombin, activates protein C. Activated protein C complexes with its cofactor protein S and inactivates FVa and FVIIIa. TFPI is a protein produced by endothelial cells that inhibits the TF:FVIIa complex and FXa. Binding to FXa is required for the inhibitory effect on TF:FVIIa. This negative feedback results in reduced subsequent thrombin generation and quenching of fibrin generation. The action of both AT and TFPI inhibits FXa during the initiation phase, leading to dependence on platelet-surface FXa generation during the propagation phase for adequate hemostasis. The fibrinolytic system also includes 2 inhibitors, principally plasminogen activator inhibitor-1 (PAI-1) and α_2-antiplasmin (α_2AP), which inhibit tPA and plasmin, respectively.

This chapter is devoted to a discussion of the pathophysiology, clinical presentation, diagnosis, prognosis, and treatment of hemostatic abnormalities, hereafter referred to as bleeding disorders. The first section reviews the approach to a patient with excessive bleeding, followed by a discussion of the specific disorders.

KEY POINTS

- Hemostasis is a complex and highly regulated process involving the subendothelium, endothelial cells, circulating cells, and plasma proteins that include both positive and negative feedback mechanisms.
- The generation of thrombin is dependent on specific protein complexes occurring on cellular surfaces: the TF:FVIIa complex at the site of injury and FIXa:FVIIIa (tenase complex) and FXa:FVa (prothrombinase complex) on the activated platelet surface.

Approach to the patient with excessive bleeding

Excessive bleeding may occur in both male and female patients of all ages and ethnicities. Symptoms can begin as early as the immediate newborn period (uncommonly, even in utero) or anytime thereafter. The bleeding symptoms experienced are related in large part to the specific factor and level of deficiency. Bleeding can be spontaneous; that is, without an identified trigger, or may occur after a hemostatic challenge, such as delivery, injury, trauma, surgery, or the onset of menstruation. Furthermore, bleeding symptoms may be confined to specific anatomic sites or may occur in multiple sites. Finally, bleeding symptoms may be present in multiple family members or may occur in the absence of a family history. All of this information is important to arrive at a correct diagnosis rapidly and with minimal, yet correctly sequenced, laboratory testing. Thus, a detailed patient and family history is a vital component of the approach to each patient with a potential bleeding disorder.

Importance of medical history

Obtaining a detailed patient and family history is crucial regardless of prior laboratory testing. The history includes a detailed discussion of specific bleeding and clinical symptoms. Information regarding bleeding symptoms should include location, frequency, and pattern, as well as duration

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both in terms of age of onset and time required for cessation. The location may suggest the part of the hemostatic system affected; patients with disorders of primary hemostasis (platelets and VWF) often experience mucocutaneous bleeding, including easy bruising, epistaxis, gingival hemorrhage with dental hygiene, heavy menstrual bleeding, and postpartum hemorrhage in women of childbearing age, whereas patients with disorders of secondary hemostasis (coagulation factor deficiencies) may experience deep-tissue bleeding, including the joints, muscles, and central nervous system. The bleeding pattern and duration of each episode, particularly for mucus membrane bleeding, assist in the determination of the likelihood of the presence of an underlying bleeding disorder. The onset of symptoms can suggest the presence of a congenital versus acquired disorder. Although congenital conditions can present at any age, it is more likely that patients with a long history of symptoms or symptoms that begin in childhood have a congenital condition, whereas patients whose onset occurs at an older age are more likely to have an acquired condition. Congenital clotting factor deficiencies that do not present until later in life do occur and include mild factor deficiencies and coagulation factor deficiencies associated with variable bleeding patterns, most notably FXI deficiency. Additional important information to be collected includes the current use of medications and herbal supplements, as these may affect the hemostatic system; the presence or absence of a family history of bleeding; a history of hemostatic challenges, including surgery, dental procedures, and trauma; and menstrual and obstetric history in females. The goal at the end of the history is to establish the likelihood of a bleeding disorder, as this guides the direction of the laboratory investigation.

Bleeding assessment tools

As discussed previously, determining the presence and severity of bleeding symptoms is a key component in evaluating a patient with a suspected bleeding disorder. However, mild bleeding symptoms are routinely reported in the "healthy" population and differentiating "pathological" from "normal" bleeding symptoms may be difficult. To meet these challenges, multiple attempts have been made to develop and validate objective frameworks for the evaluation of bleeding symptoms. Bleeding assessment tools (BATs) are standardized instruments that quantify the presence and severity of bleeding symptoms to generate a single score. The Vicenza score and its successor, the Molecular and Clinical Marker for the Diagnosis and Treatment of Type 1 von Willebrand disease (VWD) (MCMDM-1VWD), were the first to be developed and studied for patients with VWD. A pediatric version of the MCDM-1VWD was subsequently developed and included pediatric-specific questions on umbilical stump bleeding, postcircumcision bleeding, and cephalohematoma. In 2010, the International Society on Thrombosis and Haemostasis (ISTH) endorsed a consensus-based expert-administered questionnaire and grading instrument (ISTH-BAT) that provides a summated score based on 14 bleeding symptoms. ISTH-BAT may be accessed at https://www.isth.org/page/reference_tools. Given their high sensitivity and negative predictive value, BATs are useful screening instruments in cohorts with a low baseline prevalence of bleeding disorders (such as those presenting at a primary care physician office). In such cohorts, their greatest utility is in identifying patients who do not need further laboratory testing. In cohorts with a moderate-high baseline prevalence of bleeding disorders (eg, patients referred to a specialist and first-degree family members of patients with known bleeding disorders), BATs may be used in conjunction with specific laboratory tests, primarily to assess the severity of bleeding. In cohorts, BATs should not be used to determine which patients need further laboratory testing. A self-administered iteration of the ISTH-BAT (self-BAT) was recently reported and is undergoing further validation.

Screening tests

The laboratory evaluation for bleeding includes performance of initial screening tests. The most common screening tests used include platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT). When the PT or aPTT is prolonged, mixing studies are required via a 1:1 mix of patient plasma with normal pooled plasma. Test correction in the mixing study indicates a deficiency state, whereas lack of correction indicates an inhibitor, either one directed against a specific factor (eg, FVIII in acquired hemophilia) or a global inhibitor as best exemplified by a lupus anticoagulant. Inhibitors directed against FVIII in acquired hemophilia are typically time- and temperature-dependent; therefore, incubated mixing studies should be performed (incubating the patient plasma with normal standard plasma at 37°C for 1 to 2 hours). Specific factor analyses are performed after mixing studies reveal a correction of prolonged coagulation screening test(s) indicative of a deficiency state, or in the face of normal screening tests with a positive history. Screening tests are not sensitive and do not evaluate all abnormalities associated with bleeding, including VWF, FXIII, PAI-1, and α_2AP deficiencies, and may be insensitive to mild FVIII and FIX deficiencies; therefore, a patient history suggestive of a bleeding disorder may warrant testing for such deficiencies, including rare abnormalities regardless of screening test results.

Screening tests also are used to identify individuals with a high likelihood of VWD or platelet disorders. Bleeding time, once widely used, has become obsolete because of

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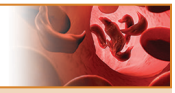
its lack of sensitivity and specificity. The platelet function analyzer PFA-100 has been proposed as having a role in screening individuals with suspected platelet dysfunction or VWD. Initial studies demonstrated the efficacy of the PFA-100 in the evaluation of patients with known severe platelet disorders or VWD. The PFA-100 induces high shear stress and simulates primary hemostasis by flowing whole blood through an aperture with a membrane coated with collagen and either adenosine diphosphate (ADP) or epinephrine. Platelets adhere to the collagen-coated surface and aggregate, forming a platelet plug that enlarges until it occludes the aperture, causing cessation of blood flow. The time to cessation of flow is recorded as closure time (CT). The sensitivity and specificity of the CT of the PFA-100 were reported as 90% for severe platelet dysfunction or VWD, with VWF plasma levels below 25%. Further details on PFA-100 may be found in Chapter 12.

It is likely that by the time patients are referred to a hematologist that some, if not all, of the previously mentioned tests may have been performed. Screening tests are sensitive to specimen handling, may vary in reliability based on laboratory, and may be influenced by medications. Repeating these laboratory tests is often required; if possible, it is best to discontinue medications known to affect their results. In summary, though screening tests are used widely to identify hemostatic abnormalities associated with bleeding, they are not perfect. The clinical suspicion for a bleeding disorder is critical to determine the extent of laboratory investigation.



KEY POINTS

- Patients with bleeding disorders occasionally present for evaluation before symptom onset, especially in the presence of a known family history or abnormal screening laboratory tests.
- Patients with bleeding disorders can present at any age with bleeding in a variety of sites. The more severe disorders tend to present earlier in life and with bleeding symptoms that often are spontaneous or in such areas as the joints, muscles, or central nervous system.
- The approach to patients with a potential bleeding disorder requires a detailed personal and family history and involves the use of screening laboratory tests, mixing studies when results are abnormal, and subsequent further specific coagulation factor testing.
- Some patients with a history or physical examination indicative of a bleeding disorder may have a normal laboratory evaluation. A study by Mezzano et al showed the diagnostic efficacy of laboratory testing in patients with hereditary mucocutaneous bleeding is approximately 40%.

Disorders of primary hemostasis

Platelet function disorders

Platelets play a key role in primary hemostasis, both by constituting the cellular structure for the primary hemostatic plug and providing a phospholipid surface upon which plasma coagulation proteins bind and form complexes. A simplified cartoon with the platelet major receptors and activation responses is shown in Figure 10-1. Platelet activation is the result of multiple signaling pathways that culminate in activation of the fibrinogen receptor integrin $\alpha_{IIb}\beta_3$, an integrin that normally exists in a resting (low-affinity) state but that transforms into an activated (high-affinity) state when stimulated by the appropriate signal transduction cascade. Activated $\alpha_{IIb}\beta_3$ then mediates platelet aggregation and promotes stable thrombus formation. This activation occurs following vascular injury when subendothelial collagen engages $\alpha_2\beta_1$ and GPVI receptors, and turbulent shear stress promotes VWF binding to GP1b-IX-V. A process known as inside-out signaling follows this platelet-surface receptor stimulation, leading to activation of $\alpha_{IIb}\beta_3$ and resulting in affinity modulation during thrombus initiation. This conformational change allows engagement of fibrinogen by multiple $\alpha_{IIb}\beta_3$ integrins, resulting in platelet aggregation. Subsequently, outside-in signaling is initiated when ligand-occupied $\alpha_{IIb}\beta_3$ integrins cluster during aggregation by binding fibrinogen, fibrin, or VWF and trigger signals that stabilize the aggregate leading to activation responses, including granule release, platelet spreading, and clot retraction. During this multistep process, platelets also become activated through binding of agonists, such as ADP or thrombin, and secrete granular contents that enhance vasoconstriction and further platelet aggregation. Finally, the platelet membrane exposes negatively charged phospholipids, the surface upon which the plasma clotting factors bind and form the fibrin meshwork. Abnormalities in platelet function can occur in any of these multitude of processes required for normal platelet function, including defects in receptor number or function, signaling, and granule content and secretion. Clinical presentation, diagnosis, and management of platelet functional disorders are discussed further in Chapter 11.

von Willebrand disease

Pathophysiology

VWD is the most common congenital bleeding disorder in humans, with an estimated prevalence of 1 in 100 individuals based on abnormal laboratory testing and 1 in 1000 individuals based on a bleeding phenotype. The

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transmission of VWD is autosomal dominant for most types but may rarely be inherited in a recessive manner (type 2N and type 3 VWD).

VWD is caused by the quantitative deficiency (type 1 and type 3) or qualitative defect (type 2) of VWF, a large, multimeric glycoprotein produced both in megakaryocytes and endothelial cells. Therefore, 2 pools of VWF are available for normal hemostasis. Circulating VWF is released from Weibel-Palade bodies within endothelial cells, whereas platelet VWF is stored in α-granules and released only upon platelet activation. The main roles of VWF in hemostasis are to (1) promote platelet adhesion to the exposed subendothelium upon vascular injury, (2) promote platelet aggregation, and (3) serve as a chaperone for FVIII in plasma, protecting it from proteolytic degradation by activated protein C (APC). VWF undergoes significant posttranslational modification, including dimerization, glycosylation, multimerization, and cleavage of the VWF propeptide (VWFpp) before being packed into storage granules (Weibel-Palade bodies or α-granules). VWFpp is released in equimolar concentrations to the mature VWF molecule, and therefore may be useful in measuring the rate of clearance of mature VWF.

When in circulation, the molecular weight of VWF ranges from 500 kDa (short VWF multimers) to 20,000 kDa (high-molecular-weight multimers [HMWM]). Molecular size is an important determinant of functional activity, as high-molecular-weight VWF multimers are the most physiologically active. The molecular weight of VWF is controlled by the metalloprotease enzyme ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin 1 motif, member 13), which cleaves VWF at the A2 domain. VWF clearance is led in part by macrophages in the liver and spleen.

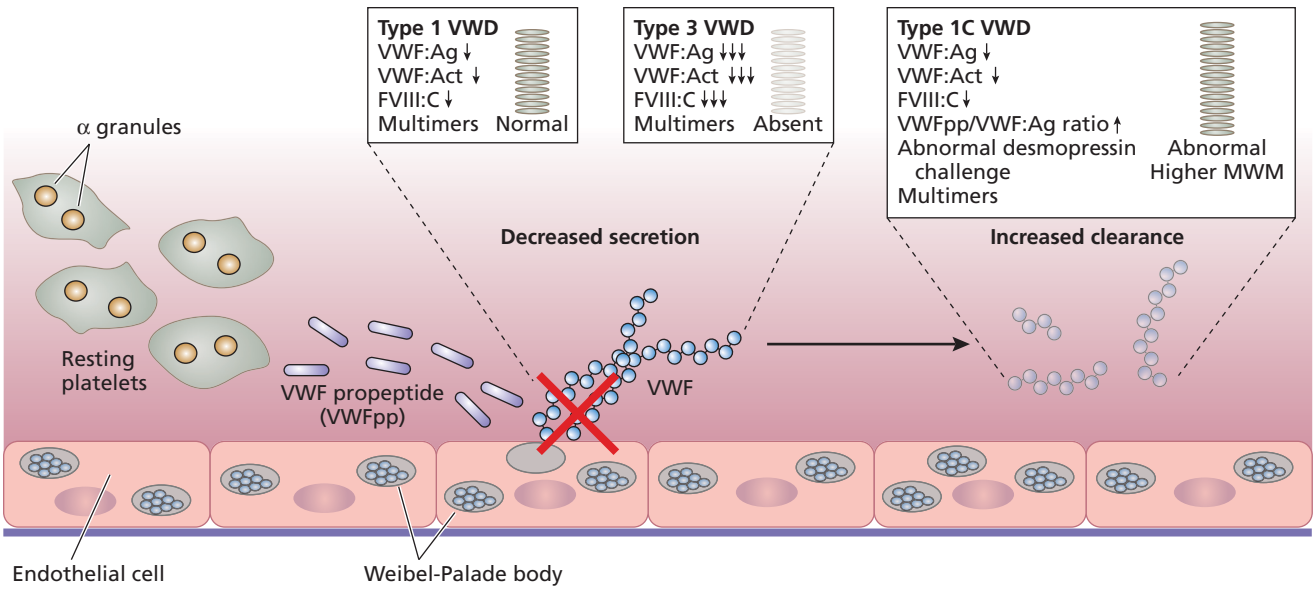
Classification of VWD

VWD is categorized into quantitative or qualitative VWF defects. VWD type 1 and type 3 represent partial and absolute quantitative deficiencies of VWF, respectively; VWD type 2 is characterized by a qualitative defect in the von Willebrand protein. The ISTH has further subdivided type 2 VWD into 4 subtypes based on the exact physiological defect: 2A, 2B, 2M, and 2N. The following is a brief description of the different subtypes and the molecular mechanisms that define them. Figures 10-4 and 10-5 illustrate these mechanisms and how they lead to the current classification. Table 10-1 describes the subtypes in more detail.

VWD type 1

VWD type 1 is defined by partial, quantitative deficiency of VWF in the setting of abnormal bleeding symptoms. A family history of the disease or personal history of bleeding symptoms is usually present, though its absence does not preclude the diagnosis. An international consensus panel has recently recommended using a VWF level <30 IU/dL (irrespective of bleeding phenotype),

Figure 10-4 Mechanisms of disease for VWD types 1 and 3. Note that the boxes show the most common laboratory findings for these types. Adapted from Branchford BR, Di Paola J, *Hematology (Am Soc Hematol Educ Program)*. 2012;2012:161-167.



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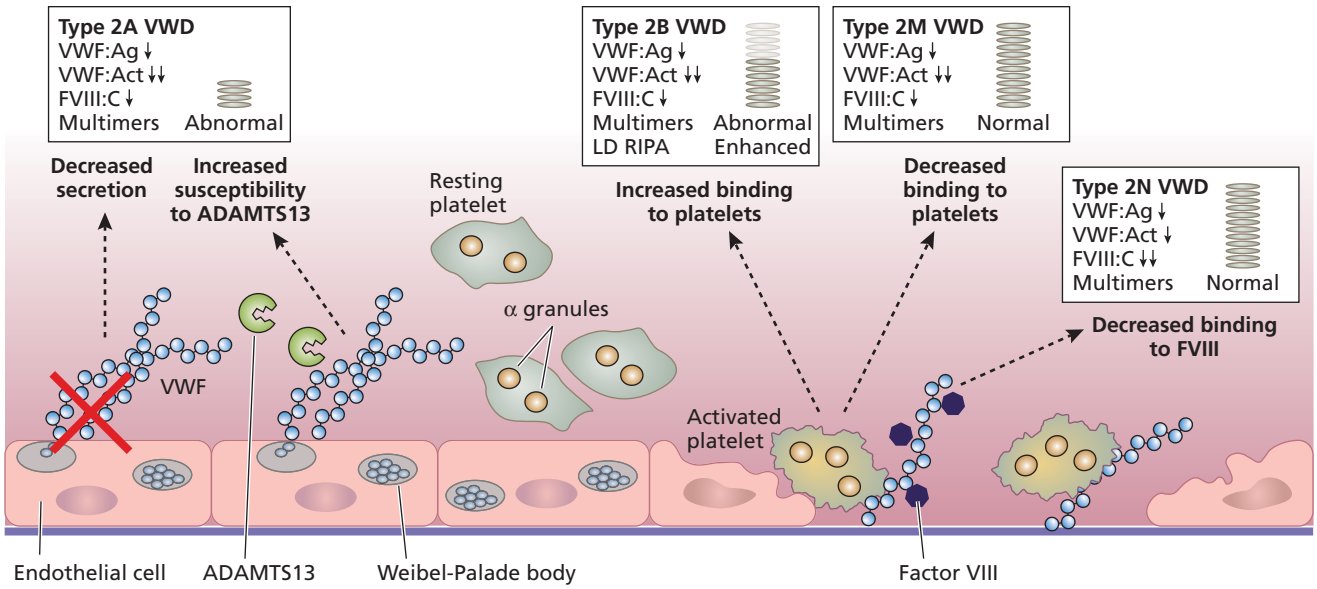

Figure 10-5 Mechanisms of disease for VWD type 2. Note that the boxes show the most common laboratory findings for the different subtypes. Adapted from Branchford BR, Di Paola J, *Hematology (Am Soc Hematol Educ Program)*. 2012;2012:161-167.

Table 10-1 Classification and diagnosis of VWD

Disease subtype	Description	VWF:Act, IU/dL	VWF:Ag, IU/dL	VWF:Act/ VWF:Ag	FVIII level	Multimer pattern
Type 1	Partial quantitative deficiency of VWF	<30 irrespective of bleeding or <50 in patients with abnormal bleeding	<30 irrespective of bleeding or <50 in patients with abnormal bleeding	≥0.70	↓ or normal	Normal
Type 2A	Defect in multimerization or increased cleavage of multimers by ADAMTS13	<50	50-200	<0.70	↓ or normal	Loss of high-molecular-weight multimers and intermediate–molecular weight multimers
Type 2B	Increased affinity for platelet GP1b	<50	50-200	<0.70	↓ or normal	Loss of high-molecular-weight multimers
Type 2M	Decreased VWF mediated platelet adhesion	<50	50-200	<0.70	↓ or normal	Normal
Type 2N	Markedly decreased binding affinity for FVIII	50-200	50-200	>0.70	↓↓	Normal
Type 3	Virtually complete deficiency of VWF	<5	<5	Not applicable	↓↓↓ <10 IU/dL	Absent

or a VWF level of <50 IU/dL in patients with abnormal bleeding to diagnose type 1 VWD. This was a major deviation from the historic National Heart Lung and Blood Institute guidelines, where patients with VWF levels between 30 and 50 IU/dL were classified as "low VWF." The change was made to ensure uniformity in diagnostic criteria across centers and to ensure access to care in patient with a bleeding phenotype given the high value placed on an explicit diagnosis.

Approximately 75% of cases of VWD type 1 result from mutations that exert a dominant negative effect by impairing the intracellular transport of VWF subunits and causing subsequent decrease in VWF secretion. A second mechanism is the rapid clearance of VWF from the

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circulation because of specific mutations in the *VWF* gene. Therefore, impaired secretion and increased clearance are likely the 2 most common molecular mechanisms that lead to VWD type 1. Of note, the probability of identifying a putative mutation in the VWF gene (*VWF*) decreases with increasing VWF levels. The variant of VWD type 1 caused by increased clearance is called type 1C. Patients with VWD type 1C have a robust initial response to desmopressin but exhibit an abrupt decrease in VWF levels (typically >30% decreased from peak VWF levels) within 2 to 4 hours, placing them at high risk for delayed postoperative hemorrhage. Because VWF is synthesized in 1:1 ratio with VWFpp, an increased VWFpp/VWF:Ag ratio also suggests increased VWF clearance. Patients with type 1C VWD have unusually large VWF multimers.

A consistent diagnostic criterion for VWD type 1 is difficult to achieve, as not all individuals who inherit a mutation in *VWF* show signs of clinical disease (a phenomenon known as low penetrance), and not all individuals that inherit the same mutation show the same clinical signs (known as variable expressivity). Individuals with blood group O have 25% to 30% lower VWF levels compared to those who have blood group A, although this variability should not affect the way that the disease is diagnosed. Additionally, plasma VWF levels increase by 10% per decade of life and may normalize for a subset of patients with prolonged follow-up. However, it is unclear whether normalization of historically low VWF levels with age also normalizes the bleeding phenotype, and such patients warrant continued follow-up and periodic reevaluation of bleeding symptoms. Lastly, VWF is an acute-phase reactant, and plasma levels may be higher during conditions of stress, inflammation, exercise, and pregnancy, and in women using oral contraceptives.

VWD type 2

VWD type 2 is characterized by qualitative defects in VWF caused by mutations in the *VWF* gene that affect the interactions of VWF with many of its ligands. VWD type 2 is subclassified into type 2A (loss of intermediate- and high–molecular weight multimers because of decreased multimerization or increased susceptibility to ADAMTS13), type 2B (gain-of-function mutation resulting in spontaneous VWF-platelet binding under physiologic shear conditions, leading to clearance of the highest-molecular-weight multimers and mild thrombocytopenia), type 2M (loss of function mutations that decrease the interaction of VWF with its platelet receptor), and type 2N (mutations in VWF causing reduced binding to FVIII, allowing for increased clearance of FVIII).

VWD type 3

VWD type 3 is inherited in an autosomal recessive manner and is characterized by complete lack of VWF protein with undetectable VWF antigen assay (VWF:Ag) and platelet-dependent VWF activity assays (VWF:Act), and resultant low FVIII:C levels (<10%), representing the steady state of FVIII in the absence of its VWF chaperone. Multimers are absent and the bleeding pattern is usually severe.

The clinical presentation of VWD includes mucocutaneous bleeding—specifically, easy and excessive bruising and bleeding from mucosal surfaces, including the nose, mouth, and gastrointestinal tract. The extent, location, and nature of bruising are important clinical points. Multiple bruises of various ages in a variety of locations are suggestive of a disorder of primary hemostasis. Similarly, epistaxis or oral-pharyngeal bleeding sufficient to result in anemia suggests the presence of a hemostatic disorder. Heavy menstrual bleeding, particularly at onset of menarche, is also suggestive of a mucocutaneous bleeding disorder. Excessive bleeding following procedures involving the mucus membranes may unmask a previously unknown bleeding disorder. The most common of these events include childbirth, oral surgery (including dental work), tonsillectomy or adenoidectomy, and sinus surgery. Some patients may present to the hematologist as a result of a documented family history of bleeding without an individual specific bleeding event. Less commonly, patients may present because of abnormal screening tests ordered before a planned procedure. Clinical manifestations may range from mild to severe. Type 2N and type 3 VWD are associated with bleeding events similar to those observed in severe hemophilia, likely because of the extremely low FVIII levels.

Diagnosis

Screening laboratory tests (complete blood count, PT, aPTT) have limited value when a diagnosis of VWD is suspected. Therefore, in clinical practice, in the face of a significant history of mucocutaneous bleeding, specific laboratory assays for VWD are required.

Diagnostic assays for VWD include quantitative measurement of the VWF antigen (VWF:Ag), platelet-dependent VWF activity (VWF:Act), and FVIII:C. The distribution of VWF multimers is also helpful to differentiate VWD type 2 subvariants. VWF:Act may be determined using the traditional VWF ristocetin cofactor assay (VWF:RCo) in which the agglutination of fixed platelets in response to patient plasma is measured in the presence of ristocetin. Important limitations of this assay include (1) a high coefficient of variation; (2) a lower level of detection of 10 to 20 IU/dL,

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which makes the accurate diagnosis of type 2 VWD difficult in patients with low VWF:Ag, as the VWF:RCo/VWF:Ag ratio becomes difficult to determine; and (3) potential for false positive results with variants that impact the ability of the VWF to bind to ristocetin but do not affect VWF activity (eg, the D1472H variant in exon 28 of the *VWF gene*). Newer functional assays such as the VWF:GP1bM, which measures the ability of patient VWF to directly bind to recombinant, mutated GP1b receptor independent of ristocetin, have been described. These assays typically have a higher reproducibility and lower coefficient of variation compared to VWF:RCo. Additionally, they are not affected by VWF variants which impact ristocetin binding. However, availability of such assays is currently limited in the United States.

Limitations exist with several of these assays. Both VWF and FVIII are acute-phase reactants and may increase 2 to 5 times above baseline because of a variety of conditions or circumstances, including infection, stress, and pregnancy. These increased levels elevate low baseline levels to within the normal range, obscuring diagnosis. Therefore, normal levels do not completely rule out VWD, especially in the face of a suspicious clinical history, and must be interpreted with caution. Performance of these assays requires an experienced coagulation laboratory, ideally with on-site processing and analysis as opposed to an experienced coagulation laboratory analyzing a "send-out" sample often drawn thousands of miles away. Because of the difficulty in ruling out this disorder with 1 normal evaluation, it is common for patients to undergo repeated testing. When local laboratory results are inconsistent, a useful strategy is to perform testing in a reference hemostasis laboratory. Finally, many preanalytic variables must be considered to accurately interpret laboratory testing. For example, refrigeration of whole-blood samples before separation can result in reduced plasma VWF levels; in addition, platelet contamination of the separated plasma may result in protease-induced VWF alterations, causing decreased activity. Given the impact of these preanalytic variables, the laboratory diagnosis of VWD should not be made based on just one set of subnormal levels.

VWF multimers are run on an agarose gel to evaluate the full range of molecular weight multimers present in the circulation. Multimeric analysis is required to differentiate between various subtypes of VWD type 2; complete absence of multimers easily identifies VWD type 3 (Figure 10-6). The FVIII:C and VWF:FVIII binding assay provide a more accurate diagnosis of VWD type 2N. Finally, the collagen-binding assay measures binding of large VWF multimers to collagen and represents an additional method to assess VWF functional activity. This assay

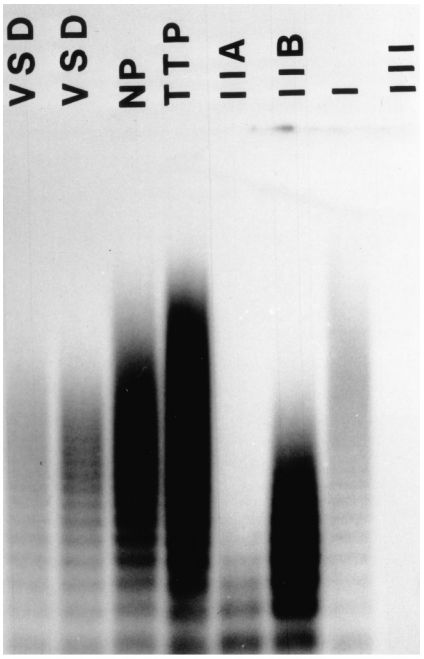

Figure 10-6 Representation of a VWF multimer analysis. The third column from the left represents normal plasma, as indicated by the NP at the top of the column. In type 2A VWD, there is a loss of high- and intermediate-weight multimers as indicated by the loss of the bands in the gel under the heading. In type 2B VWD, there is a loss of high-molecular-weight multimers. In type 1, all the multimers are present but in reduced amounts, as can be seen by the presence of all the bands but with more faint staining than seen in normal plasma. In type 3 disease, there is a complete absence of multimers, and no staining of bands is visible. The column labeled VSD stands for ventricular-septal defect, a condition that results in acquired von Willebrand syndrome with the loss of multimers of all sizes. The column labeled TTP stands for thrombotic thrombocytopenic purpura, in which ultralarge multimers can be observed.

recently gained attention when it was reported that several families with abnormal bleeding symptoms have mutations in the VWF collagen-binding site with preserved VWF:Ag and VWF:Act. The collagen-binding assay does not require the use of ristocetin, but studies have reported that the type of collagen employed influences the results. Lastly, low-dose ristocetin-induced platelet aggregation (LD-RIPA) may be used to identify abnormally increased binding of VWF to platelets, as occurs in type 2B.

Laboratory test results are compatible with VWD type 1 if the levels of both VWF:Act (eg, VWF:GP1bM, VWF:RCo) and VWF:Ag are <30 IU/dL (<50 IU/dL in symptomatic patients) and the plasma VWF multimer distribution is normal, though the intensity may be reduced because of lower amount of protein. Additionally, the VWF:Act/VWF:Ag ratio approximates 1. In patients with

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VWD type 1C, the VWF:Ag and VWF:Act levels are low, and in most cases the multimer assay is characterized by the presence of abnormally large high-molecular-weight forms. As this subtype is characterized by rapid VWF clearance, most patients exhibit an abnormal desmopressin challenge. Additionally, a VWFpp level allows for discrimination of VWD type 1C through the VWFpp/VWF:Ag ratio (in patients with VWD type 1C, the ratio is typically >3). While recent consensus guidelines advise relying on desmopressin challenge results (see the following text) to make the diagnosis of VWD type 1C, the VWFpp/VWF:Ag ratio remains a useful adjunct.

VWD type 2 is a qualitative defect caused by mutations in VWF that result in abnormal interactions with several of its ligands. The diagnosis of type 2A is made in the presence of a low VWF:Ag and a disproportionately low VWF:Act, with pronounced loss of both high– and intermediate–molecular weight multimers. The VWF:Act/VWF:Ag ratio is less than 0.70. Type 2M is caused by mutations in the VWF binding site for platelet glycoprotein 1ba (GPIb), with resultant decreased binding of VWF to GPIb and subsequent impairment of platelet-dependent function. The multimer structure and distribution are normal. Type 2B results from gain-of-function mutations in the VWF binding site for platelet GPIb, leading to the formation of rapidly cleared platelet-VWF complexes. Type 2B VWD is also associated with loss of HMWM. LD-RIPA can be used to confirm this subtype, where a level of ristocetin insufficient to promote platelet binding with normal VWF causes enhanced platelet agglutination in the presence of gain-of-function mutations. While LD-RIPA can still be informative, current guidelines recommend targeted genetic sequencing in patients with suspected type 2B VWD. This is because LD-RIPA can show similar results in patients with platelet-type VWD (a rare disorder analogous to VWF type 2B, though the culprit mutation and dysfunctional ligand is platelet GPIb rather than in VWF). It is important to differentiate these 2 entities, as treatment approaches are significantly different. VWD type 2B is treated with VWF concentrates, whereas platelet-type VWD is treated with platelet transfusions. For the evaluation of platelet-type VWD, the patient's platelets can be tested with a normal exogenous VWF substrate in a ristocetin-induced platelet-agglutination-based mixing study. Enhanced binding confirms the diagnosis. Finally, type 2N is characterized by mutations in the FVIII binding site of VWF, disturbing the normal interaction of these 2 proteins. Patients with VWD type 2N may exhibit normal or decreased VWF:Ag and VWF:Act with disproportionately decreased FVIII:C, which may be misclassified as mild hemophilia A. Specific VWF:FVIII binding assays are used to confirm the diagnosis of type 2N. Symptomatic patients are either homozygous or compound heterozygous for mutations in the *VWF* gene. Patients with a prior diagnosis of mild FVIII deficiency who do not respond well to recombinant FVIII infusions or belong to families for whom the inheritance appears to be autosomal dominant should be evaluated for VWD type 2N.

VWD type 3 is characterized by undetectable VWF:Ag and VWF:Act levels, FVIII:C levels commonly <10%, and lack of multimers. A description of the laboratory pattern for each subtype is shown in Table 10-1.

Genetic testing

Sequencing of the *VWF* gene is challenging because of its large size, highly polymorphic structure, and presence of a homologous partial pseudogene on chromosome 22. Additionally, identifying a genetic basis for VWD type 1, the most common variant, is particularly difficult, with population-based epidemiological studies identifying a putative mutation in only ~65% of tested subjects. Therefore, gene sequencing for diagnosis is currently reserved for specific cases in which these test results likely contribute significantly to diagnosis and management, particularly in cases in which treatment options vary based on diagnosis. Genetic testing can be used to differentiate type 2B from platelet-type VWD, mild hemophilia A from VWD type 2N, and to subclassify VWD type 2. Genetic testing may be also justified in VWD type 3 because large deletions may predispose to the development of inhibitory antibodies and anaphylactic reactions.

Acquired von Willebrand syndrome

Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder with clinical symptoms and laboratory abnormalities similar to congenital VWD. It is characterized by an older age at onset of bleeding symptoms and a lack of family history of bleeding. While the exact pathophysiology is unclear, 5 distinct mechanisms have been proposed: (1) decreased production of VWF (eg, hypothyroidism); (2) autoantibodies against VWF and immune complex formation (eg, systemic lupus erythematosus, Hashimoto thyroiditis); (3) adsorption of VWF to tumor cells (eg, Wilms tumor, lymphoproliferative disorders); (4) drug-mediated proteolysis of HMWM (eg, ciprofloxacin); and (5) increased proteolysis of HMWM under pathological high-shear-stress conditions (eg, congenital heart disease, aortic stenosis [Heyde syndrome], extracorporeal devices, mechanical valves). Treatment of underlying medical disorders, such as surgery and chemotherapy for Wilms tumor, replacement therapy for hypothyroidism, immune suppression for systemic lupus erythematosus, and surgical correction of

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cardiac defects, usually results in rapid resolution of symptoms. Intravenous immune globulin (IVIG) may also be effective in patients with immune-mediated AVWS.

Treatment

The principle for management of VWD is to increase or replace VWF to achieve hemostasis. This is accomplished with either medications that cause the release of endogenous stores of VWF into the circulation (desmopressin) or the use of recombinant or plasma-derived VWF concentrates.

Mild-to-moderate bleeding associated with VWD type 1 often is managed with desmopressin. Desmopressin, a synthetic analog of the antidiuretic hormone vasopressin, exerts its hemostatic effect by stimulating secretion of stored VWF from Weibel-Palade bodies in endothelial cells into the plasma. Desmopressin may be administered intravenously, subcutaneously, or intranasally (Stimate; CSL Behring, King of Prussia, PA). The standard dose of desmopressin is 0.3 μg/kg administered intravenously or subcutaneously or 300 μg administered intranasally. A desmopressin challenge test should be performed to document a hemostatic response in VWD. The challenge test entails measurement of VWF:Ag, VWF:Act, and FVIII:C at baseline, followed by repeat measurements at 1 and 4 hours after administration of desmopressin. The 4-hour postdesmopressin results help identify patients with increased VWF clearance as observed in VWD type 1C. A desmopressin response is defined as a 2-fold increase in baseline VWF levels, with sustained increase in VWF and FVIII levels >50 IU/dL for 4 hours. Approximately 80% of patients with VWD type 1 respond with hemostatic levels, although responses can still vary and should be measured to determine the adequacy of desmopressin for specific hemostatic challenges. Repeated administration of desmopressin may lead to tachyphylaxis, with blunted responses likely resulting from depletion of the VWF storage pool. Repeated doses also increase the risk of hyponatremia given the drug's effect on free water handling by the kidneys. Thus, use of desmopressin no more than once daily and for no more than 2 or 3 consecutive days serves as an acceptable clinical guideline for home use. To avoid hyponatremia, patients should be instructed to limit their fluid intake for 24 hours after desmopressin use. There are some reports of the benefits of desmopressin in VWD type 2; in general, it is less effective in these subtypes. Desmopressin in contraindicated in patients with type 2B VWD and platelet-type VWD as it may precipitate significant thrombocytopenia. It is also ineffective in patients with type 3 VWD where treatment primarily entails the use of replacement therapy with VWF concentrates. Desmopressin is additionally contraindicated in children <2 years old, patients with seizure disorders, and patients with active cardiovascular disease.

Several products available in the United States contain intact VWF, including Humate-P (CSL Behring, King of Prussia, PA), Alphanate (Grifols Biologicals, Los Angeles, CA), Koāte DVI (Talecris, Research Triangle Park, NC), and Wilate (Octapharma, Lachen, Switzerland), with similar products available in other countries. These plasma-derived concentrates contain VWF and FVIII in varying ratios and with variable amounts of multimer size or distribution. Humate-P and Wilate are approved by the United States Food and Drug Administration (FDA) for both on-demand treatment of bleeding and prevention of perioperative hemorrhage in patients with VWD, while Alphanate is approved only for prevention of perioperative hemorrhage. Although these products are manufactured via processes that include viral attenuation and inactivation steps, a theoretical risk of infectious pathogen transmission exists. A recombinant form of VWF, Vonvendi (Shire, Bannockburn, IL) has also been approved by the FDA for management of VWD in adults. Since this product contains no FVIII, it is recommended that patients with FVIII levels <40% also receive recombinant FVIII with the first dose of Vonvendi. Subsequently, the Vonvendi may be administered exclusively, since endogenous FVIII production is able to maintain hemostatic levels of FVIII within 6 hours of the first infusion of Vonvendi. In patients with VWD and a history of frequent and severe bleeding, long-term prophylaxis with VWF concentrates may be considered. Prophylaxis regimens remain largely empiric and should be guided by careful laboratory assessment.

Antifibrinolytic agents (aminocaproic acid [EACA] and *tranexamic acid*) are useful adjunctive therapies to both desmopressin and VWF concentrates. These agents, which are lysine analogs, inhibit plasmin-mediated thrombolysis and exert their effect through clot stabilization and prevention of early dissolution. Thus, these agents may be effective in prevention of rebleeding, a common problem in individuals with bleeding disorders, especially in areas with increased fibrinolysis, such as the oral mucosa or gastrointestinal tract. Antifibrinolytics may be administered intravenously, orally, or topically in amenable circumstances, and are used either therapeutically for bleeding or prophylactically as part of perioperative management. Antifibrinolytic agents have been used widely for many years, have a well-documented and favorable safety profile, and are well-tolerated in most patients. Commonly reported side effects include headache and abdominal discomfort; however, these symptoms do not preclude its continued use if ameliorated with other agents, such as acetaminophen. Antifibrinolytic agents

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should be used with caution in patients with a history of thrombosis or atherosclerosis and are contraindicated when hematuria is present because of the risk for obstructive uropathy secondary to ureteral clots.

Contraceptive agents, including combined oral contraceptives and levonorgestrel intrauterine devices, can be effective therapies for the management of heavy menstrual bleeding. TXA may also be used for management of heavy menstrual bleeding, particularly in patients who wish to conceive. Patients with mild mucocutaneous bleeding episodes may be managed with topical adjunctive measures such as compression, gelatin sponge or gauze soaked in TXA for superficial wounds, or nasal packing and topical thrombin gel for epistaxis. Case reports have described the use of recombinant factor VIIa (rFVIIa) in VWD; these are limited to patients with type 3 disease with inhibitors to VWF and patients with AVWS.

In addition to treatment with hemostatic agents, education of patients and primary care providers is important so that bleeding episodes are either prevented or recognized early and managed locally. Lifestyle modifications are important and include avoidance of collision and contact sports, routine dental care, use of medical-alert-bracelets and avoidance of platelet-impairing medications (eg, aspirin, NSAIDs). Patients should be advised to report their condition to physicians before undergoing any invasive procedures so that appropriate prophylactic measures can be used.

Gaps in knowledge

The most challenging aspect in the management of VWD is the establishment of an accurate diagnosis, particularly in type 1 disease. This can be especially difficult because VWF levels may appear normal because of the associated clinical circumstances, despite a clinical history suggestive of a bleeding disorder. Future research aimed at the development of laboratory assays with improved performance characteristics to decrease variability and diagnostic dilemmas is needed. A wide variation in bleeding symptoms exists among patients within the same disease subtype, likely because of genetic modifiers of the bleeding phenotype. Overall, currently available therapies are effective; however, it is not completely clear under what circumstances specific therapies are best applied to achieve an optimal outcome. There are few prospective comparative therapy studies to guide physicians in determining the risks and benefits of available therapies. Diagnostic and therapeutic guidelines developed by a collaboration by the American Society of Hematology, International Society on Thrombosis and Haemostasias, the National Hemophilia Foundation, and the World Federation of Hemophilia are based on the best available evidence and expert opinion.

KEY POINTS

- VWD is the most common inherited bleeding disorder in the general population.
- VWD is divided into several subtypes. Type 1 is the most common, encompassing 2/3 of cases.
- Laboratory diagnosis of VWD may be difficult, especially in type 1.
- VWD treatment is based on the subtype; the most common agents used for treatment include desmopressin, antifibrinolytics, hormonal therapy for heavy menstrual bleeding, and VWF concentrates for severe bleeding or in types 2 and 3.

Disorders of secondary hemostasis

Congenital hemophilia A and B (FVIII and FIX deficiency)

Overview

The most frequently encountered bleeding disorders associated with factor deficiencies are hemophilia A and B (FVIII and FIX deficiency, respectively). The previous review on the physiology of hemostasis emphasized the critical roles played by FVIII and FIX in generating the thrombin burst leading to fibrin clot formation. Deficiency of either FVIII or FIX results in reduced formation of the intrinsic tenase complex (FIXa:FVIIIa), and thus reduced formation of FXa and thrombin on the surface of activated platelets at injured vasculature. The extrinsic tenase complex (TF:FVIIa) remains able to generate small amounts of FXa and thrombin, though often to a degree insufficient to prevent bleeding. Inadequate thrombin generation leads to fibrin clots with poor structural integrity, as can be visualized by electron microscopy; specifically, formation of large, coarse fibrin strands as opposed to normal thinner strands that form a tight network is observed. In addition, reduced thrombin generation results in decreased formation of activated FXIII and TAFI, both of which result in a clot less resistant to normal fibrinolysis. Therefore, deficiencies of FVIII or FIX result in poorly formed clots that are more susceptible to fibrinolysis, clinically observed as the bleeding manifestations in hemophilia.

Molecular basis of congenital hemophilia A and B

Congenital deficiencies of FVIII and FIX occur as a result of genetic mutations in *F8* and *F9* genes, respectively, both located on the long arm of the X chromosome. Accordingly, these deficiencies are most commonly

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observed in males because of their hemizygous state. Although more than 2100 unique mutations have been associated with hemophilia A. The most common mutation, occurring in up to 45% of patients with severe hemophilia A, is the intron 22 inversion, caused by homologous recombination between the 9.5 kb sequence within intron 22 of the *F8* gene and 1 of 2 extragenic homologous regions. As a result, exons 1 to 22 are inverted and separated from exons 23 to 26. Other *F8* mutations include small and large deletions, missense, nonsense, and splice-site mutations in nearly all of the coding areas of *F8*. More than 1100 unique mutations have been associated with hemophilia B, with missense mutations predominating (58% of cases). Hemophilia B Leyden is a noteworthy variant that results from mutation of the *F9* promoter region, preventing normal binding of transcription factors upstream of the *F9* gene. During puberty, higher androgen levels facilitate binding of the androgen receptor to the *F9* promoter, overcoming the Leyden mutation and allowing transcription of the *F9* gene. This can lead to spontaneous increases in FIX plasma levels and abrogation of the abnormal bleeding phenotype during and after puberty.

Female carriers of 1 or more *F8* or *F9* mutations can have highly variable ranges of factor activity and bleeding symptoms. Deficiencies significant enough to cause abnormal bleeding symptoms can be because of skewed X-chromosome inactivation (Barr bodies) or the presence of other genetic abnormalities, such as Turner syndrome or X-autosomal translocations. Care should therefore be taken not to dismiss the possibility of hemophilia carrier status in females describing unusual bleeding symptoms. Newly revised nomenclature for females with *F8* or *F9* mutations reinforces this point; if FVIII or FIX activity levels are <40%, they are classified the same as males with hemophilia (mild, moderate, or severe). In females with FVIII or FIX activity >40%, they are designated as either symptomatic or asymptomatic carriers. A wide range of *F8* and *F9* mutations have been described, and the mutation type (deletion, inversion, missense, or nonsense) and specific area of the protein affected determines the severity of disease. In approximately 25% of cases, no family history is identified. In such cases, the affected individual's mother is either not a carrier and the de novo mutation arose after conception of the affected male child, or the mother is a carrier as a result of a germline mutation at the time of the mother's conception.

The My Life, Our Future (MLOF) project is a multi-institutional collaboration and repository for genetic data volunteered by persons with hemophilia (PwH). Since its inception in 2012, MLOF has accumulated more than 9000 individual patient samples and now serves as an important resource for genetic research.

Clinical presentation

The clinical presentation of congenital hemophilia, including the severity of bleeds and the onset of initial bleeding episode, is highly variable and correlates with the degree of factor deficiency in plasma. Severity of hemophilia is classified based on the functional activity of the deficient factor: <1% is severe, 1% to 5% is moderate, and 6% to 40% is mild. FVIII and FIX activities of >40% are considered normal (Table 10-2). While this classification scheme is helpful for informing decisions about treatment (eg, individuals with <1% factor activity benefit the most from prophylactic factor replacement), it is critical to carefully consider each individual's particular bleeding phenotype, as some patients with factor activities in the moderate and occasionally mild range can experience bleeding at a frequency expected of far more severe disease. This phenotypic variability can be influenced by variables such as coinheritance of other hemostatic defects, presence of either inherited or acquired thrombophilias, use of medications affecting hemostasis, and level of physical activity, among others.

Knowing the biologic sex of the fetus in pregnant female hemophilia carriers is critical, since male infants born with hemophilia can be at risk for bleeding complications before the diagnosis can be confirmed. In particular, the incidence of intracranial hemorrhage (ICH) in male infants with hemophilia has been reported to be as high as 4%. While methods to determine the genotype of the fetus in utero do exist (amniocentesis, chorionic villus sampling), it is generally recommended that obstetricians manage delivery of male infants as if the child has hemophilia. This includes early consultation with maternal-fetal medicine or high-risk obstetrics services, predelivery administration of hemostatic agents to the mother, and planning for atraumatic delivery by avoiding the use of forceps or vacuum extraction. The safety of vaginal versus cesarean delivery has not been compared in a randomized trial; thus, either may be used.

Bleeding in neonates and infants with hemophilia is most commonly encountered with circumcision, heel sticks for laboratory draws, medication injections, or invasive procedures. As noted previously, care must also be taken to recognize ICH. Across all severities, approximately

Table 10-2 Hemophilia A and B severity classification

	FVIII/FIX activity, IU/dL	Spontaneous bleeding
Unaffected	>40%	No
Mild	6%-40%	Rare
Moderate	1%-5%	Occasional
Severe	<1%	Frequent

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70% of hemophilia diagnoses are made within the first 1 month of life, with the remainder of diagnosis mostly by 24 months of age. Upon reaching adolescence, increased weight-bearing and physical activity leads to more frequent intra-articular, intramuscular, and other soft-tissue bleeding. Bleeding symptoms can occur spontaneously in individuals with severe hemophilia, whereas moderate hemophilia has a variable age of presentation; diagnosis may be established from a known family history, in the newborn period because of bleeding, or later in life (even as an adult) with a bleeding event associated with intercurrent injury or invasive procedure. Mild hemophilia (factor activity levels between 6% and 40%) may be diagnosed at ages similar to moderate hemophilia. In the absence of a family history, patients with mild hemophilia typically present later in childhood or during the teenage or adult years with bleeding associated with injury or surgery rather than spontaneous hemorrhage.

Special attention should be paid to hemarthrosis, which constitutes 80% of bleeding manifestations in adults with hemophilia and can be highly morbid, even if appropriately treated. Joints with repeated bleeding develop acute or chronic synovitis, followed by articular damage; a *target joint* is one in which repeated bleeding (3 or more bleeds during a 6-month period) occurs. Orthopedic surgery, including total prosthetic joint replacement, may be indicated with severely affected joints to alleviate pain and mobility issues; data suggest favorable rates of knee joint hardware removal-free survival (80% to 90% at 20 years postoperative).

The discovery of FVIII's roles in physiologic pathways distinct from hemostasis have raised the specter of other clinical manifestations of hemophilia A, including dysregulated angiogenesis and bone turnover; research is ongoing to clarify the clinical significance of these questions, germane because of the recent emergence of nonfactor hemostatic therapies (eg, emicizumab) for hemophilia.

Diagnosis

Laboratory diagnosis of hemophilia begins with screening coagulation studies, including PT and aPTT. A normal aPTT, however, does not unequivocally indicate the absence of hemophilia and may be within normal reference range in patients with mild deficiencies in FVIII and FIX (Figure 10-7). After identification of a prolonged aPTT, a 1:1 mixing study with patient plasma and normal pooled plasma is performed. Immediate and sustained correction of the prolongated aPTT points to a factor deficiency. No correction, or immediate correction followed by recurrent prolongation, suggests a factor inhibitor (see the section "Inhibitors in hemophilia"). Specific

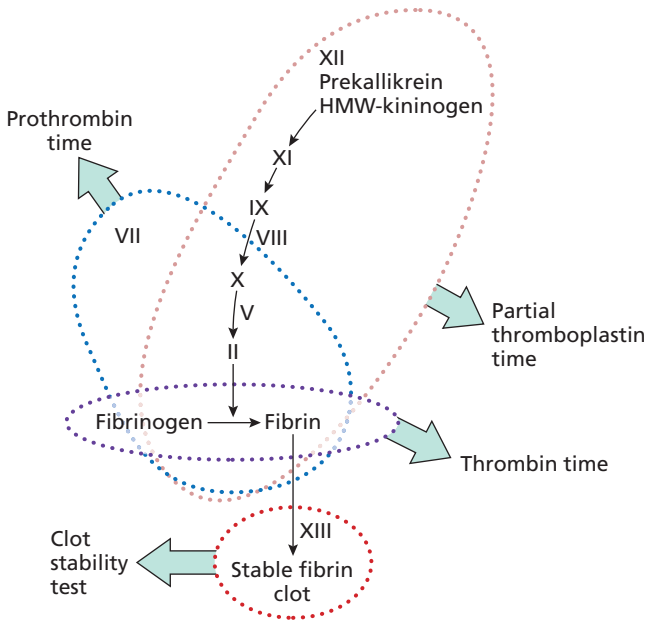

Figure 10-7 Plasma coagulation reactions in in vitro laboratory assays. Factor XII, prekallikrein, and high-molecular-weight kininogen are required for a normal activated partial thromboplastin time but not for normal in vivo hemostasis. This diagram outlines the coagulation factors required for each of 4 basic tests that characterize the coagulation cascade: prothrombin time, activated partial thromboplastin time, thrombin time, and FXIII assay.

factor activity assays are then used to identify the deficient factor. In the setting of an isolated prolonged aPTT, FVIII, FIX, FXI, and VWF should be assayed.

There are 2 methods by which the factor activity can be measured: a one-stage assay (OSA) and a two-stage chromogenic assay (CSA) (Table 10-3). The OSA is based on the principles of the aPTT, in which patient plasma is combined with phospholipid, calcium, and a contact activator (eg, kaolin, silica, ellagic acid) and the time it takes for the analyzer to detect a fibrin clot is measured. The OSA remains the most widely available and frequently used assay for measuring factor activity in the United States, as it is relatively simple to perform, rapid, and inexpensive. An observation of critical importance is the fact that the OSA is rendered inaccurate by the presence of the bispecific antibody emicizumab. Low circulating plasma levels of emicizumab result in significant shortening of the aPTT and unexpectedly high levels of FVIII:C by OSA. For further reading, see Chapter 12, Laboratory hematology.

The two-stage chromogenic factor activity assay (CSA) is based on the detection of fluorescence generated by a chromogenic FXa substrate. The CSA can potentially

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Table 10-3 Comparing the one-stage and two-stage (chromogenic) factor activity assays

	One-stage assay (OSA)	Two-stage, chromogenic assay (CSA)
Mechanism	Clot-based assay (similar to aPTT, measures time to analyzer detection of fibrin clot) Mix of patient plasma with reference factor-deficient plasma Compares patient with reference curve to determine factor activity	Chromogenic assay (measures fluorescence of chromogenic FXa substrate upon enzymatic cleavage) 1st stage, generation of FXa; 2nd stage, addition of chromogenic FXa substrate No reference plasma necessary
Reagents required	Reference, factor-deficient plasma	Factor-deficient plasma unnecessary
Variability in results	High interlaboratory variation	Low interlaboratory variation
Lupus anticoagulant effect	May falsely lower measured factor activity	Unaffected
Emicizumab effect	Falsely elevates FVIII:C	Human reagents: measures emicizumab effect Bovine reagents: isolates measurement of endogenous or administered FVIII
Availability	Common	Limited (more common in Europe)

aPTT, activated partial thromboplastin time.

overcome the limitations posed by emicizumab; given the specificity of emicizumab for human coagulation factors, bovine-sourced reagents can be used instead to measure endogenous FVIII:C and the activity of administered factor products. Conversely, using human reagents for the CSA can estimate the equivalent FVIII activity conferred by emicizumab alone (Table 10-4). While CSA assays are becoming more commonly available, particularly in Europe, they often remain limited to reference labs in the United States. For further reading, see Chapter 12 (Laboratory hematology).

Significant discrepancies between FVIII:C based on either the OSA and CSA have been identified in up to 1/3 of patients with mild and moderate hemophilia. The reason for the discrepancy lies in the underlying *F8* mutation. Mutations that affect FVIII cleavage by thrombin result in higher FVIII:C levels where CSA>OSA, because the relatively longer incubation period of the CSA allows for more FVIII cleavage by thrombin. Conversely, mutations that reduce FVIII stability yield FVIII:C levels where CSA<OSA, because of degradation of the FVIII during the longer CSA incubation period. As a result, major guidelines suggest performing both the OSA and CSA for the diagnosis of hemophilia A, particularly in cases of suspected mild disease. At a minimum, one needs to consider performing the alternative FVIII assay if the clinical picture is not consistent with the assay result. Interestingly, discrepancies between the OSA and CSA have also been discovered in patients who have received gene therapy for hemophilia A, with 1 study consistently demonstrating OSA results ~1.6-fold higher than CSA results; the cause remains unknown.

Ultimately, the type and severity of hemophilia are established based on the FVIII or FIX assay. As previously discussed, appropriate specimen procurement and handling are critical to obtaining accurate results. In newborns, where cord blood is tested because of a known family history, levels may be altered based on sample procurement, level of deficiency, and neonatal variations, as seen with decreases in vitamin K–dependent clotting factors. Therefore, repeat testing may be required based on cord blood results and their concordance with expected results and clinical symptoms. In addition, assaying factor activity levels at the lowest range of the curve is technically difficult, and sample analysis through a reference laboratory may aid differentiation of the severe from moderate forms. Finally, because FVIII is an acute-phase reactant, obtaining a true baseline level may be difficult for patients with moderate and mild deficiencies when tested in the setting of inflammation.

Treatment

Clotting factor concentrates

The mainstay of hemophilia treatment is replacement of the deficient coagulation factor, though this simple concept has seen substantial evolution over the past several decades. Currently both recombinant and plasma-derived clotting factor concentrates (CFCs) are available to treat both FVIII and FIX deficiency (Tables 10-5 and 10-6). The choice of the specific product used includes consideration of availability, cost, manufacturing method, delivery system, and half-life. While both plasma-derived and recombinant CFCs are equally effective for prophylaxis and treatment of bleeds, some data suggest a higher incidence of FVIII inhibitor development with recombinant CFCs; for a more detailed discussion, see the section "Inhibitors in hemophilia."

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Table 10-4 Laboratory assays in the presence of emicizumab

Measurement of:	Preferred assay	Comments
Emicizumab "activity"	CSA using *human* FIXa and FX reagents	Also measures concurrent exogenously administered FVIII
Endogenous and exogenously administered FVIII:C in the presence of emicizumab	CSA using *bovine* FIXa and FX reagents	
FVIII inhibitor in presence of emicizumab	Chromogenic Bethesda assay using *bovine* reagents	

An important advance in hemophilia treatment has been the development of extended half-life (EHL) CFCs. These modifications generally increase stability and/or reduce clearance of the administered factor through one of several methods including fusion of FVIII to albumin, immunoglobulin Fc fragments, and polyethylene glycol (PEG). Efforts to extend the half-life of clotting factors have been less successful with FVIII than FIX because the large size of the FVIII protein, smaller volume of distribution restricted to the intravascular space, and clearance dictated in large part by VWF. Thus, EHL modifications have yielded approximately 1.5-fold increase in FVIII product half-life, and a 4- to 5-fold increase in FIX product half-life. Clinical trials are also ongoing for a novel FVIII EHL (BIVV001) with half-life comparable to FIX EHLs. Importantly, while EHL products have demonstrated significant reductions in the number of infusions needed to maintain specific trough factor activity levels, no major differences in efficacy or safety have been discovered between standard half-life and EHL products, including similar rates of inhibitor development. Therefore, decisions to use EHL products should closely consider specific patient characteristics and treatment preferences. Similar to issues with emicizumab, an emerging discovery has been the variability in factor activity depending on the specific EHL product and the type of activity assay

Table 10-5 Factor VIII concentrates currently available in the United States

Brand name	Generation	FVIII molecule	Modification	Half-life, h	Production cell line	Stability at RT, mo
Plasma-derived						
Monoclate	N/A	Full length	—	~12	N/A	None
Hemophil M	N/A	Full length	—	~12	N/A	None
Recombinant standard half-life						
Recombinate	1st	Full length	—	15	CHO	None
Kogenate FS	2nd	Full length	—	13.7	BHK	3
Advate	3rd	Full length	—	12	CHO	6
Xyntha	3rd	B domain-deleted	—	11.2	CHO	6
NovoEight	3rd	B domain-truncated	—	10.8	CHO	6
Kovaltry	3rd	Full length	—	14.3	BHK	12
Afstyla	3rd	B domain-truncated	Single chain	14.5	CHO	3
Nuwiq	4th	B domain-deleted	—	17.1	HEK	3
Recombinant extended half-life						
Adynovate	3rd	Full length	PEGylated	14.3	CHO	1
Eloctate	4th	B domain-deleted	Fc-fused	19	HEK	6
Esperoct		B domain-truncated	glycoPEGylated	18	CHO	12
Jivi		B domain-deleted	PEGylated	19	BHK	6

Other FVIII concentrates approved for use in FVIII deficiency (Alphanate, Wilate, Humate-P) also contain von Willebrand factor and should not be routinely used for hemophilia specifically.

BHK, baby hamster kidney; CHO, Chinese hamster ovary; HEK, human embryonic kidney; N/A, not applicable; RT, room temperature.

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Table 10-6 Factor IX concentrates currently available in the United States

Brand name	Modification	Recovery, IU/kg per IU/dL	Half-life, h	Production cell line	Stability at RT, mo
Plasma derived					
Mononine	—	1.0	22.6	N/A	1
Alphanine	—	N/A	21	N/A	1
Recombinant standard half-life					
Benefix	—	0.7	19.4	CHO	24
Ixinity	—	0.98	24	CHO	
Rixubis	—	0.9	25.4	CHO	36
Recombinant extended half-life					
Alprolix	Fc-fused	1.12	97	HEK	6
Rebinyn*	glycoPEGylated	2.34	83	CHO	6
Idelvion	Albumin-fused	1.3	104	CHO	24

CHO, Chinese hamster ovary; HEK, human embryonic kidney; N/A, not available/applicable; PEG, polyethylene glycol; RT, room temperature.

*Indicated for on-demand therapy only.

(OSA versus CSA) and well as variability between different reagents used for these assays.

For all FVIII CFCs, 1 IU/kg typically increases the FVIII level by 2%. Therefore, a typical empiric FVIII CFC dose is 50 IU/kg, which is expected to raise the factor activity from <1% (at the most extreme) to 100%. Tailored doses can be administered if a patient's baseline factor activity level is well-known. Infusions of nonmodified FVIII products can be repeated as needed approximately every 8 to 12 hours, the average half-life of the FVIII protein. For FIX CFCs, a general rule of thumb is that for every 1 IU/kg infused, FIX levels will increase by 1%, though this varies slightly depending on the specific FIX CFC. For instance, many unmodified, recombinant FIX CFCs increase FIX by only 0.7%-0.8%, with children exhibiting a lower recovery compared with adults. A typical empiric FIX CFC dose is still approximately 100 IU/kg, which will raise FIX activity close to 100% in a severe patient. Dosing of FIX CFCs should be repeated every 12-24 hours as needed for acute bleeds. The generally longer half-life of FIX is mainly caused by its large volume of distribution including in the extravascular space. The FDA label for each specific CFC product includes information on the most appropriate factor activity assay to use to monitor therapy.

Prophylaxis with clotting factor concentrates

Hemophilia treatment approaches are divided into 2 main categories: prophylaxis and on-demand. Prophylaxis is the regular infusion of CFCs to prevent bleeding events. Primary prophylaxis is defined as the initiation of regular, continuous factor replacement therapy starting before or shortly after the first episode of hemarthrosis and before the age of 3 years. Prophylactic strategies aim to maintain FVIII or FIX activity levels >1%, thereby converting "severe" patients to a moderate phenotype, minimizing the chances of spontaneous bleeding. This strategy has been shown to substantially reduce the morbidity of bleeding, particularly hemarthrosis and the development of chronic hemophilic arthropathy. Accumulating data, however, has revealed that occult hemarthrosis still occurs despite maintenance of factor levels >1%, and suggests that more intensive prophylaxis aiming for higher factor activity troughs may be superior at preventing bleeds and joint damage. This finding requires additional corroboration, but also careful consideration of escalating healthcare costs and burden to the patient.

Primary prophylaxis is considered the standard of care for patients with severe hemophilia. Full-dose prophylaxis entails the administration of standard half-life factor concentrates every other day for hemophilia A, or twice a week for hemophilia B. These regimens can be time- and resource-intensive and often require central venous access in younger children who have not yet learned to self-cannulate. An alternative approach to full-dose, primary prophylaxis is to use escalating dose and frequency of prophylaxis. Such an approach starts patients on once-a-week factor infusions and escalates therapy based on bleeding symptoms. Once primary prophylaxis has been instituted, most patients should continue indefinitely. A subset of patients (~25%) may be able to discontinue prophylaxis in adulthood while maintaining a low rate of bleeding, though this mandates careful discussion with patients about the risks of major bleeding prior to attempting.

Secondary prophylaxis is the regular infusion of factor replacement initiated after 2 or more episodes of

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hemarthrosis, but before the presence of joint disease on physical examination or imaging studies. The goal is to interrupt a bleeding pattern and prevent joint damage through suppression of bleeding episodes. Tertiary prophylaxis is when regular infusions of factor replacement are started after the onset of joint disease seen on examination or imaging studies; this strategy typically applies to previously untreated adults. Studies of tertiary prophylaxis have demonstrated improvements in bleeding frequency, quality of life, and joint pain symptoms, though the prospective, randomized SPINART trial showed that preexisting joint damage as seen on MRI remained unchanged. Administration of CFCs to prevent bleeding only prior to circumstances that place patients at high risk for bleeding, such as before sports or other physical activities, may be appropriate in patients unwilling to follow a continuous prophylaxis regimen or for those with nonsevere disease who historically bleed when participating in these types of activities. It must also be emphasized that while primary prophylaxis is used most frequently in patients with severe disease, it can also be applied to patients with moderate disease (ie, FVIII:C between 1% to 5%) depending on their individual bleeding phenotype. The best dose for prophylaxis varies according to a variety of factors, which include but are not limited to the product used, the age of the patient (younger patients have low recovery and shorter half-life), and the patient's joint status and activity level.

While empiric prophylaxis protocols have been successfully used for many years, a one-size-fits-all approach is not ideal given the observed variability in factor level recovery among different patients and within individual patients over time, as well as the abundance of CFC products available, each with different pharmacokinetic (PK) profiles. One solution to this problem has been the development of population PK-guided prophylaxis regimens. Several web-based tools have been developed that draw on large databases of population PK data and other covariates (eg, age, body mass, blood group, VWF levels). These tools are then able to model factor recovery and decay curves for individual patients based on only a few factor activity measurements after a CFC dose, and results can then be applied to *any* CFC including EHL products. While clinical benefits of PK-guided CFC dosing remain under investigation, reductions in overall CFC use have been seen in small studies.

Prophylaxis with emicizumab in hemophilia A

In addition to CFCs, emicizumab (Hemlibra, Roche, Basel, Switzerland) is also approved for prophylaxis of bleeding in patients with severe hemophilia A, with or without inhibitors to FVIII (see the following section on inhibitors). Emicizumab is a chimeric, humanized, bispecific monoclonal antibody with affinity for both FIX/FIXa and FX, and functions by bringing these clotting factors into close proximity to form an artificial intrinsic tenase complex. While emicizumab functions in a similar manner to natural FVIII in this way, emicizumab has a much lower affinity for its substrates and lacks the negative feedback regulation of natural FVIII. Emicizumab is administered subcutaneously and can be dosed anywhere from once per week to once per month. Compared to bleeding prophylaxis with CFCs, emicizumab provides a potentially more convenient prophylaxis strategy. Four major prospective randomized clinical trials (HAVEN 1-4) have demonstrated the efficacy and safety of emicizumab in both children and adults with severe hemophilia, with and without preexisting FVIII inhibitors, showing statistically significant reductions in annualized bleeding rate (ABR) compared to CFC prophylaxis or no prophylactic therapy in all tested populations.

Attempts to quantify the "FVIII equivalency" of emicizumab have generated a wide range of results, with a general consensus of 10% to 30% equivalent FVIII:C, though this remains an imperfect estimate and should not be used to justify withholding additional hemostatic treatments in the setting of breakthrough bleeding or major surgery. Thus, patients treated with emicizumab still require traditional CFCs (either factor-specific or a bypassing agent) in these scenarios and should generally be treated similarly to patients not on emicizumab. One notable exception is in PwH A and FVIII inhibitors treated with emicizumab, in whom the use of high doses of factor eight inhibitor bypassing activity (FEIBA) has been associated with development of thrombotic microangiopathy. While dosing recommendations for FEIBA in these patients have since been modified, rFVIIa products remain the bypassing agent of choice for these patients.

Studies investigating the appropriate perioperative management of patients treated with emicizumab are ongoing. In general, patients undergoing major surgery should be managed similarly to any patient with moderate/severe hemophilia and given CFCs perioperatively to ensure adequate hemostasis. Retrospective data suggest this to be a generally safe strategy. Reports have also been published of *minor* surgeries being safely performed in patients on emicizumab without the addition of any other hemostatic therapies. More data is needed to better risk stratify patients in these scenarios.

Treatment: on-demand therapy

On-demand therapy refers to the use of CFCs after bleeding occurs. This treatment approach does not require

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regular infusions with their associated issues (cost and need for frequent intravenous access) and is less expensive in the short run, but is ineffective at preventing joint disease. This mode of therapy now is used primarily for patients with moderate and mild hemophilia because of the infrequency of bleeding events and the associated low risk of joint disease. Rarely, patients with severe hemophilia have infrequent bleeding events and can be managed with on-demand therapy, with or without prophylactic infusions prior to specific activities. It is generally recommended, however, to target factor activities of at least 50% for acute bleeds, surgery, and delivery, though higher goals closer to 100% are often desired for particularly critical sites of bleeding including intracranial, throat/neck, and gastrointestinal. Treatment duration with CFCs is generally continued until the bleeding resolves. This can be anywhere from a single infusion for a mild bleeding event (eg, provoked superficial bruising), up to several weeks for more severe bleeding events (eg, ICH or intramuscular hematoma).

Adjunctive therapy for hemophilia is similar to that discussed for VWD. Patients with mild hemophilia A may be treated with desmopressin after a challenge dose demonstrates a hemostatic response; the response level dictates the type of bleeding events that may be treated with this agent. Antifibrinolytic agents are efficacious for mucosal bleeding and are useful used in conjunction with CFCs or desmopressin, particularly for dental work or oral surgery. For women with hemophilia who experience heavy menstrual bleeding, hormonal contraceptives can be helpful.

Inhibitors in hemophilia

Overview

A significant complication of hemophilia after exposure to replacement therapy is the development of immunoglobulin G autoantibodies that bind and neutralize FVIII or FIX, termed *inhibitors*. Inhibitors render standard treatment with CFCs ineffective and result in hemorrhagic episodes that are prolonged and more difficult to control, with associated increased risk of morbidity and mortality. The lifetime incidence of inhibitor development is between 20% and 30% in severe hemophilia A; 5% to 10% in mild or moderate hemophilia A; and 3% to 5% in hemophilia B. Inhibitors form because of immune naivety to the FVIII or FIX protein, and subsequent recognition of infused CFCs as foreign. It is rare for inhibitors to develop beyond the first 75 exposure days to CFCs; 79% of inhibitors occur within the first 20 exposure days. Risk factors for inhibitor development include both patient and treatment characteristics. Because of the greater prevalence of hemophilia A and higher incidence of inhibitors in this population, more is known about risk factors for inhibitor development than for hemophilia B.

Besides hemophilia severity, other notable patient-specific risk factors for inhibitor development include the specific *F8* gene mutation (more common with large gene deletions), ethnicity (more common in Black African and Hispanic ancestry), and family history of inhibitors. Certain polymorphisms of immune response genes (IL10, TNF-alpha, and CTLA-4) have also been implicated. Treatment-related risk factors include the source, timing, and intensity of the CFC product used. This is best illustrated by the findings of the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) trial, in which previously untreated PwH (severe) under the age of 6 were randomized to either a plasma-derived or recombinant product, under a prophylactic or on-demand treatment strategy at the discretion of the treating physician. In the 251 analyzed patients, an inhibitor developed in 26.8% that received plasma-derived products versus 44.5% of patients that received recombinant products. One theory is that the recombinant product lacked VWF and thus had less allosteric masking of FVIII epitopes. The generalizability of this study remains uncertain, and major guidelines do not recommend one form of CFC over another. Other treatment-related risk factors include receipt of intensive replacement therapy (5 or more consecutive days) or surgery during early factor exposure.

Inhibitor development in hemophilia B is far less common and has not been shown to be influenced by type of CFC used. Two unique consequences of inhibitors in this population are worth noting. First, up to 50% of patients with inhibitors to FIX may develop anaphylactoid or true anaphylactic reactions when receiving factor products containing FIX, particularly with null *F9* mutations. Second, the same patients who experience anaphylaxis can also develop nephrotic syndrome with prolonged, high-dose exposure to FIX-containing CFCs. The pathomechanism of both of these manifestations remains speculative, though it is advised to avoid FIX-containing products for these patients (see following section on treatment of inhibitors).

Inhibitors are stratified by severity into 2 categories: low and high titer. Titers are measured via the Bethesda inhibitor assay, with results reported in Bethesda units (BU) per mL. Low-titer inhibitors are <5 BU/mL despite repeated exposure to factor replacement, whereas high-titer inhibitors are >5 BU/mL at any time, regardless of the current titer. The distinction between low and high-titer inhibitors is critical when deciding on appropriate therapy and prophylaxis for bleeds, as well as potential inhibitor eradication. Patient with high-titer inhibitors may exhibit a

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decrease in inhibitor titer, sometime to undetectable levels, upon complete withdrawal of the specific clotting factor. With subsequent exposure to the deficient factor, these patients can mount an anamnestic response whereby their inhibitor will increase within 7 to 10 days of factor exposure. Therefore, patients with previously high-titer inhibitors that have fallen to low or undetectable levels should only be treated with CFCs containing FVIII with extreme caution and close observation for anamnesis. Patients with low-titer inhibitors can still be managed with higher doses of CFCs to overcome the inhibitor and achieve a hemostatic factor level. Approximately 10% of low-titer inhibitors resolve without intervention (often within a few weeks) and are termed *transient inhibitors;* therefore, ongoing measurement of inhibitor titers is critical.

Treatment considerations in patients with inhibitors

The 2 pillars of management of patients with high-titer inhibitors include: (1) treatment and prevention of bleeding and (2) inhibitor eradication. The management of bleeding episodes in inhibitor patients can be challenging, with the majority of hemophilia-related morbidity in the United States occurring in patients with high-titer inhibitors. Options for bleeding treatment and prophylaxis in patients with persistently high-titer inhibitors include bypassing agents or emicizumab. Three bypassing agents are currently licensed in the United States: activated prothrombin complex concentrate (APCC) (FEIBA; Baxter, Deerfield, IL), rFVIIa (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark), and coagulation factor VIIa (recombinant)-jncw (SevenFact; LFB S.A., Les Ulis, France). APCC (hereafter referred to as FEIBA) is a plasma-derived concentrate consisting of the vitamin K–dependent clotting factors both in nonactivated and activated forms. FEIBA's mechanism of action is largely attributed to FXa and prothrombin, although this product also contains FIXa and FVIIa. As described previously, caution should be exercised when using FEIBA in patients with hemophilia B and FIX inhibitors because of the risk of anaphylaxis and/or nephrotic syndrome, as well as in patients currently treated with emicizumab (see section on emicizumab).

Two recombinant FVIIa-based bypassing agents are available for treatment of patients with hemophilia and inhibitors, NovoSeven and SevenFact. The mechanism of action of both of these agents is via TF-independent FXa and thrombin generation on the surface of activated platelets. SevenFact is only approved for use in patients ≥12 years old. Both FEIBA and rFVIIa products are similarly effective; prospective studies have shown 70% to 90% effectiveness at treating bleeding episodes. FEIBA and NovoSeven also have abundant data supporting their safety; the incidence of thrombosis when using these agents at their recommended doses has been <1% in clinical trials. In addition, FEIBA as a plasma-derived product has an excellent safety record without documented viral transmission.

The most important consideration when choosing a product in an inhibitor patient is its ability to achieve rapid bleed control and thereby limit morbidity and mortality. Thus, product choice is individualized. Because APCC is an FIX-based product, its use in FIX inhibitor patients with infusion-associated reactions is contraindicated. APCC may contain small quantities of FVIII and result in continued stimulation of the inhibitor titer in FVIII-deficient patients. Accordingly, a rFVIIa product that does not contain FVIII or FIX does not lead to anamnesis and may be preferred if trying to allow the inhibitor to reach a low level before attempting inhibitor eradication (see following section on immune tolerance induction [ITI]). Management of acute bleeding is critical; therefore, inhibitor stimulation is not an absolute contraindication to APCC use during this time if any bleeding episode is unresponsive to rFVIIa. Dosing regimens for these products been established (Table 10-7). Occasionally, patients present with bleeding events refractory to all bypassing agents. In such cases, combining FEIBA and rFVIIa has been reported using a sequential regimen. Alternatively, FEIBA or rFVIIa can be dosed based on results of global hemostatic assays (thrombin generation assay or thromboelastography). Although these approaches have been effective and safe in a small number of young children, the reports remain anecdotal.

Historically, the prevention of bleeding in inhibitor patients has been more challenging. Several prospective studies have demonstrated the successful use of rFVIIa for both minor and major surgery. This has led to an increased availability of required surgical procedures in inhibitor patients, most notably orthopedic procedures for amelioration of hemophilic arthropathy. FEIBA has been used in the surgical setting, but the body of reports supporting its use, dosing, and safety is smaller compared to rFVIIa. It is important to mention that the risk of thrombosis may increase with the sequential use of rFVIIa and FEIBA.

Routine prophylaxis with bypassing agents to prevent bleeding episodes in inhibitor patients has become more common. Several studies have demonstrated the utility of this strategy. FEIBA (85 U/kg, 3 to 3.5 times per week) has demonstrated a 62% to 72.5% reduction in the frequency of bleeding events. However, the response was variable with up to 38% having minimal to no change

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Table 10-7 Bypassing agents and typical dosing based on bleed site or clinical context

Agent	Joint/muscle	Life or limb threatening	Perioperative	Prophylaxis
APCC (FEIBA) †	50-100 U/kg	100 U/kg	50-100 U/kg	85 U/kg every other day
Frequency	Repeat every 6 to 12 hours as needed	Repeat every 6 to 12 hours as needed	Repeat every 6 to 12 hours as needed	—
rFVIIa (NovoSeven)	90 μg/kg	90 μg/kg	90 μg/kg	††90 μg/kg/day
Frequency	Repeat every 2 hours as needed	Repeat every 2 hours as needed	Repeat every 2 hours as needed†††	Repeat daily
rFVIIa (SevenFact)	75 mcg/kg	225 mcg/kg	—	—
Frequency	Repeat every 3 hours as needed	Repeat dosing at 75 mcg/kg every 3 hours as needed, starting 6 hours after initial dose	—	—

APCC, activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.

†Doses >200 U/kg/day should be avoided.

††rFVIIa remains off-label for bleeding prophylaxis.

†††Frequency and duration vary according to the type of surgery. Refer to prescribing information.

in bleeding frequency. rFVIIa prophylaxis has been studied at 2 doses—90 and 270 μg/kg daily—and led to 45% and 59% reductions in bleeding frequency, respectively, compared to pre-rFVIIa rates. Although prophylaxis with bypassing agents has demonstrated benefit, it is less than that seen with tertiary prophylaxis using factor replacement therapy in noninhibitor patients and is more difficult to achieve, since FEIBA is typically a large infusion volume and rFVIIa products are require frequent dosing. Prophylaxis with emicizumab in patients with severe *hemophilia A* and inhibitors has been previously discussed.

Despite the availability of hemostatic agents for patients with inhibitors, inhibitor eradication remains an important consideration to restore the capacity to use FVIII CFCs for treatment of bleeding. ITI involves regular administration of the deficient factor to reset the immune system by inducing peripheral tolerance. Hay and DiMichele completed and published an international prospective ITI study in good-risk patients. This study compared daily high-dose FVIII (200 IU/kg) to low-dose FVIII (50 IU/kg) 3 times weekly. The study was stopped before reaching the planned endpoint because of an increased rate of bleeding observed in patients receiving FVIII 50 IU/kg 3 times weekly. Typical ITI regimens are therefore anywhere from 100 to 200 IU/kg given once daily. The complete response rate of ITI is approximately 70% to 80% (defined as negative Bethesda inhibitor titer, factor recovery >66% and half-life >6 hours for standard FVIII CFCs). Several meta-analyses have demonstrated similar success rates regardless of specific FVIII CFC used, and while standard-half-life CFCs remain preferred, data for EHL CFCs for ITI are accumulating.

Clinical studies have identified several factors associated with ITI success, including the historical peak inhibitor titer (<200 BU/mL), titer at start of therapy (<10 BU/mL), peak titer after the start of ITI (<100 BU/mL), age at initiation (<8 years), and time from inhibitor development to ITI start (<2 years). It is best to initiate ITI when the titer is <10 BU/mL, although this must be balanced against the risk of delaying tolerance and persistent risk of bleeding. For those who fail an initial course of ITI, the rate of success with a second ITI course is unknown. Options to consider include using a VWF-containing FVIII product or adding rituximab, though clear evidence to guide treatment decisions is lacking. The best approach to inhibitor eradication in patients with nonsevere hemophilia is also unclear. In general, patients with nonsevere hemophilia do not respond to ITI as well as patients with severe disease. Rituximab without ITI has also been used and may lead to more rapid inhibitor eradication than observation alone.

Because of the associated risk of anaphylactic reactions and nephrotic syndrome in patients with hemophilia B and inhibitors, ITI may not be possible or, if undertaken, requires desensitization to FIX. The overall success rate of ITI in FIX deficiency is 35%, far lower than the 75% achieved in FVIII deficiency. Thus, although fewer FIX inhibitor patients exist, they remain a significant treatment challenge for practitioners.

Gene therapy and other nonfactor treatments for hemophilia

CFCs, bypassing agents and emicizumab all aim to restore normal hemostasis by providing exogenous mechanisms to replace the deficient clotting factor. Gene therapy, however, represents a novel and potentially curative strategy that could theoretically render continuous hemostatic agent administration unnecessary. While no gene therapy products are yet licensed by the FDA for use in patients with hemophilia, several products for both hemophilia A and B are currently undergoing clinical trials. All current hemophilia gene therapy products under development use a

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similar overall framework: recombinant technology is used to package modified FVIII or FIX genetic sequences into adeno-associated virus (AAV) vectors engineered to exhibit tropism for hepatocytes. The product is intravenously infused, with the viral vectors then delivering their transgene products to hepatocytes, and host nuclear machinery expresses the factor products. Natural infection with wild-type AAV is common during childhood, thus most gene therapy clinical trials have excluded patients with preexisting neutralizing antibodies to AAV. Despite the AAV capsid being engineered to be less immunogenic, a prominent issue with gene therapy trials has been the development in treated patients of immune responses to the AAV vector, resulting in detectable transaminitis and occasionally loss of FVIII/FIX activity because of hepatocyte death. This outcome can be mitigated with close monitoring and prompt initiation of immune suppression with corticosteroids, though more research on viral vectors is needed. In most published clinical trials of gene therapy, treatment has resulted in significant early increases in factor levels, enough to convert most patients from severe to moderate/mild phenotypes and substantially reducing ABR. However, gradual loss of factor activity over time has been near universal and remains a significant limitation of current gene therapy products. In one early phase clinical trial of a FVIII gene therapy product, mean FVIII:C at 1, 2, and 3 years postinfusion was 64%, 36%, and 33%, respectively, leading the FDA to request additional data prior to consideration of approval. FIX gene therapy products have seen relatively greater success, which may be partially explained by differences in characteristics of the FVIII and FIX transgenes. The cost of gene therapy treatments has also garnered attention, though will need to be more carefully analyzed and compared to the costs of lifetime of CFC and other hemostatic agents.

Other novel treatment strategies for hemophilia A and B include agents that either amplify normal procoagulant, or inhibit normal anticoagulant, pathways. Concizumab is a monoclonal antibody against TFPI, which promotes thrombin generation by disinhibiting tissue factor (extrinsic) pathway activity. Two phase 2 clinical trials (explorer 4 and 5) evaluated the efficacy and safety of daily, subcutaneous concizumab in patients with severe hemophilia A and B with and without inhibitors and found significantly reduced ABR compared to on-demand therapy. Two paired phase 3 clinical trials (explorer 7 and 8) were briefly paused because of the occurrence of several nonfatal thromboembolic events in concizumab-treated subjects, though the trial has since resumed under new guidelines for concurrent hemostatic agent use. Fitusiran is an RNA-interfering (RNAi) compound targeting and reducing synthesis of antithrombin, thereby abolishing a prominent, natural anticoagulant mechanism. This investigational agent has also generated concern because of nonfatal thrombotic episodes diagnosed in an early clinical trial, though protocols for ongoing clinical trials have similarly been developed to mitigate this risk. The position of concizumab, fitusiran, and other investigational hemostatic agents within the hemophilia treatment armamentarium remains to be seen, given the concurrent rapid development of emicizumab and gene therapy.

Prognosis and outcomes

Currently, PwH without inhibitors and treated on a prophylactic regimen have an excellent prognosis and lead near-normal lives. A Swedish cohort followed for nearly 40 years substantiates these outcomes. For PwH and inhibitors, the outcome is more variable, and the risk of morbidity is significant. When ITI is successful, the outcome can be converted to that of a noninhibitor patient, yet the morbidity experienced depends on the amount of joint disease and other bleeding events that occurred before ITI success. It is likely that many of these patients have experienced hemarthroses, muscle, or even intracranial hemorrhage and that some of these bleeding events are associated with permanent sequelae. For inhibitor patients in whom ITI was not successful or not performed, significant musculoskeletal morbidity is common, resulting in permanent disability and poor quality of life. With improved hemostatic coverage available for surgical interventions, even PwH and inhibitors now may undergo procedures to reduce pain and increase functionality. Combined with the increased use of prophylaxis, it is possible now to develop treatment strategies to ameliorate the consequences of recurrent bleeding and allow patients to lead more productive lives.

Gaps in knowledge

The greatest challenge with the potential for significant reward lies with gene therapy, a potentially curative approach. As previously discussed, additional research is needed to determine the appropriate patient eligibility, timing, and type of gene therapy before it can be routinely encouraged. Another approach deserving of future work is the prevention of inhibitor formation. An improved understanding of the immunologic pathways involved in inhibitor formation and development of tolerance would open avenues to prevent inhibitor development or increase the rate of tolerance achieved. It is conceivable that an approach could be developed to program the immune system to induce tolerance before or in association with exposure to CFCs. Future research efforts could lead to the development of replacement products that are less, or perhaps not at all, immunogenic. In inhibitor

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patients, methods to perform ITI in FIX deficiency lag behind those for FVIII deficiency. For patients with anaphylactoid reactions, options for desensitization and subsequent ITI are limited, with an overall poor outcome, although rare successes have been reported. The FIX-deficient inhibitor population with anaphylactoid reactions represents a small, vulnerable population with only 1 therapeutic agent presently available for the management of bleeding episodes; new approaches and treatments are clearly required. Finally, the continued evolution of our comfort with using emicizumab, ideally based on prospective clinical trials, will hopefully involve more knowledge regarding perioperative hemostatic management, use concurrently with other hemostatic agents, and safety in physically active patients.

KEY POINTS

- Hemophilia is an X-linked bleeding disorder resulting from deficiencies of FVIII or FIX and is categorized as mild, moderate, or severe depending on the factor activity level.
- Patients with severe hemophilia are most notably at risk for developing hemophilic arthropathy, but this can be mitigated with regular, prophylactic CFC infusions begun at an early age.
- Many FVIII and FIX CFCs are available to treat and prevent bleeding episodes and are highly effective, though require intravenous access.
- Patients with hemophilia, especially those with severe disease, may develop neutralizing antibodies directed against the deficient factor, termed inhibitors. Inhibitors can be high- or low-responding types, with higher titers rendering traditional CFC therapy ineffective.
- Inhibitors can be eradicated with ITI in approximately 70% of patients with hemophilia A, but success depends on several patient- and disease-related factors.
- Patients with high-responding inhibitors are infused with bypassing agents to treat or prevent bleeding episodes. Alternatively, emicizumab may be administered subcutaneously to prevent bleeding episodes.
- Gene therapy is a groundbreaking development in hemophilia treatment, though it remains limited to clinical trials, and questions remain on its long-term durability and cost-effectiveness.

Acquired hemophilia

Pathophysiology and etiology

Rarely, hemophilia can be acquired upon formation of autoantibodies to clotting factors, most commonly FVIII. This is termed acquired hemophilia A (AHA). AHA has been associated with a variety of conditions, including pregnancy, malignancies, and autoimmune diseases, though half of cases can remain idiopathic. Overall, the annual incidence is 1.4 per million, and occurs in 2 peaks; 1 associated with pregnancy and the other with older age (>60). The median age of onset is approximately 77 years. The anti-FVIII autoantibodies inhibit the functional activity of endogenous FVIII, resulting in a bleeding diathesis.

Clinical presentation

AHA may present with the dramatic onset of spontaneous bleeding, though can also initially be detected with an asymptomatically prolonged aPTT. Bleeding is typically mucocutaneous, gastrointestinal, intramuscular, genitourinary, or retroperitoneal. ICH has been reported but remains rare. Although some of these bleeding symptoms are similar to congenital hemophilia, the incidence of hemarthroses in AHA is low. Additionally, bleeding in patients with AHA may be more severe than is seen in congenital hemophilia, despite similar FVIII levels (see the following section on diagnosis) In the era of routine use of bypassing agents, fatal bleeding is reported in 3% to 9% of patients.

Diagnosis

AHA should be suspected in adult patients that present with bleeding symptoms and a prolonged aPTT. Rarely, patients first present with an asymptomatically prolonged aPTT. Thus, evaluation of a prolonged aPTT in an adult should be worked up regardless of the presence or absence of bleeding. In half of AHA cases, FVIII:C levels are <1%. However, unlike in congenital hemophilia, the inhibitors in AHA often exhibit type 2 kinetics and incompletely neutralize FVIII. This translates to unreliable correlation between factor and Bethesda inhibitor assay results and bleeding symptoms. Caution must therefore be taken to avoid false reassurance in the face of laboratory tests that would otherwise place the patient in the category of "mild/moderate hemophilia" or having a "low-titer" inhibitor if the patient had congenital hemophilia. Once the diagnosis of AHA has been made, attention must also be directed to identifying any potential associated medical conditions. At a minimum, age-appropriate cancer screening and evaluation for pregnancy should be undertaken, though additional workup including serum protein electrophoresis, autoimmune disease markers, and cross-sectional imaging may be considered on a case-by-case basis.

Treatment

Bleeding treatment and prophylaxis

The management of bleeding episodes in AHA is similar in many respects to that of congenital hemophilia with inhibitors, and the principles outlined earlier largely apply.

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A notable exception is the 2% to 5% reported incidence of thromboembolic events with use of bypassing agents, significantly higher than that reported for congenital hemophilia with inhibitors. This risk is particularly high in older patients and may therefore reflect the higher prevalence of other traditional thrombotic risk factors in this age group. Approved bypassing agents for AHA similarly include APCC (FEIBA) and rFVIIa (only NovoSeven is approved for this indication). An additional hemostatic agent approved for AHA is recombinant porcine FVIII (Obizur; Baxalta, Westlake Village, CA). Autoantibodies to human FVIII cross-react with porcine FVIII in approximately 40% of cases, more commonly when Bethesda inhibitor titers are >100 BU/mL. This still leaves a significant proportion of patients with AHA who can potentially be treated with porcine FVIII, which benefits from being a true FVIII protein and theoretically more effective at bleeding control than bypassing agents and can be measured with standard one-stage factor activity assays. In a single-arm, phase 2/3 study in 28 patients with AHA and major bleeding, treatment with porcine FVIII effectively controlled bleeding in 86% of cases and was safe. More recent data also suggest that porcine FVIII may be effective even in those with autoantibodies exhibiting cross-reactivity to porcine FVIII. The FDA approved starting dose is 200 IU/kg, though algorithms using starting doses of 100 IU/kg have successfully been implemented and reported in small case series. While guidelines continue to recommend measuring baseline anti-porcine FVIII antibody titers prior to consideration of treatment with porcine FVIII, more studies are needed to determine the relevance of these findings. Finally, emicizumab monotherapy has demonstrated efficacy for treatment of bleeding in AHA; in a series of 12 patients, emicizumab effectively controlled bleeding in all patients, even in those who had demonstrated continued bleeding despite bypassing agents. Larger studies are needed to determine the appropriate implementation of emicizumab in AHA.

Inhibitor eradication

Strategies to promote inhibitor eradication in acquired hemophilia are distinct from congenital hemophilia with inhibitors. Because AHA is caused by the development of autoantibodies that result from loss of self-tolerance, it tends to respond to immunosuppressive medications effective for autoimmune disorders in general. Corticosteroids are considered first-line therapy and should be used even in patients without current bleeding symptoms. Patients with detectable FVIII levels and inhibitor concentrations of <20 BU/mL may respond to corticosteroids alone. Patients with inhibitor titers of >20 BU/mL are less likely to respond to corticosteroids alone, and inhibitor eradication can be more successful with the addition of cyclophosphamide. Given the high morbidity and mortality associated with infections because of immune suppression in these patients, risk stratification is essential and careful attention should be paid to any infectious symptoms. Overall, complete remission (undetectable inhibitor titer and FVIII >50%) can be achieved in 60% to 80% of patients after a median of 5 to 6 weeks. The role of rituximab for up-front therapy remains controversial and is generally reserved for second-line therapy. Although registry data do not indicate that rituximab increases the response rate, there is some evidence that it may reduce the rate of relapse. Since patients with acquired hemophilia continue to produce their own FVIII, ITI protocols used for congenital hemophilia with inhibitors do not have a role in AHA. Relapses occur in approximately 10% to 20% of patients, most often during the first year, and thus ongoing monitoring is essential.

Rare factor deficiencies

Deficiencies of other coagulation factors that play a role in thrombin generation, cross-linking, and stabilization of the fibrin clot, or disruption of normal fibrinolysis, may also lead to a bleeding diathesis. Deficiencies of fibrinogen, factor II (prothrombin), FV, FVII, FX, and FXIII result in bleeding disorders. FXII deficiency, while prolonging the aPTT, is not associated with an abnormal bleeding tendency. The rare factor deficiencies are distinguished from the more common FVIII and FIX deficiencies are by generally inconsistent correlation between severity of the bleeding and factor levels (Table 10-8). In addition, both quantitative and qualitative (functional) deficiencies can be seen. Although FVIII and FIX deficiency are defined as rare disorders affecting approximately 20,000 Americans, deficiencies of these other coagulation factors are far less common. Therefore, the clinical presentation related to any specific level and the range of symptoms experienced are less well described than in hemophilia A and B. Bleeding symptoms for rare factor deficiencies are most commonly encountered in the setting of delivery in women and invasive procedures, but spontaneous, sometimes life-threatening bleeding can also occur. Much of the data describing rare factor deficiencies in humans comes from a retrospective study by the European Network of Rare Bleeding Disorders.

Fibrinogen disorders

Pathophysiology

Congenital disorders of fibrinogen are caused by defects in the genes *FGA, FGB,* and *FGG* and can be inherited both in autosomal dominant and recessive patterns.

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Table 10-8 Bleeding sites and symptoms and factor replacement choices for rare factor deficiencies

Factor deficiency (level associated with major bleeding)*	Bleeding sites	Other symptoms	Factor replacement	Acquired deficiencies
Fibrinogen (<10 mg/dL)	Delayed bleeding postoperatively	Splenic rupture Miscarriage Thrombosis	Fibrinogen concentrate: (RiaStap or Fibryga) Cryoprecipitate	Liver disease Asparaginase therapy DIC
Prothrombin (<10%)	Hemarthrosis	None	PCC	Vitamin K deficiency Vitamin K antagonists Liver disease Lupus anticoagulant
Factor V (<10%)	No typical sites	None	FFP Platelet transfusion	Topical bovine thrombin exposure
Factor VII (<10%)	Intracranial	Thrombosis	rFVIIa PCC	Vitamin K deficiency Liver disease Vitamin K antagonists and "superwarfarins"
Factor X (<10%)	Intracranial	None	PCC	Vitamin K deficiency Vitamin K antagonists Liver disease AL amyloidosis
Factor XI (no clear association between levels and bleeding)	Surgery, mucocutaneous	None	FFP FXI concentrates (not approved in United States)	Autoantibodies (rare)
Factor XIII (<15%)	Intracranial Umbilical stump	Poor wound healing Miscarriage	pdFXIII concentrate (Corifact) rFXIII A subunit (Tretten) FFP, cryoprecipitate	Cardiopulmonary bypass Inflammatory bowel disease

RiaStap and Fibryga are licensed for congenital afibrinogenemia. Recombinant factor VIIa (NovoSeven) is licensed for the treatment of congenital FVII deficiency. Corifact and Tretten are licensed for congenital FXIII deficiency. Prothrombin complex concentrates (PCC) not licensed for the treatment of rare factor deficiencies and contain variable amounts of factors II, VII, and X, with dosing based on FIX units.

DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma.

*Official Communication of the Scientific Subcommittee on Rare Bleeding Disorders of the ISTH.

Quantitative fibrinogen disorders include congenital afibrinogenemia which typically occurs secondary to homozygous mutations in the *FGA* gene, with less severe deficiency (hypofibrinogenemia) resulting from heterozygous mutations in fibrinogen genes. Dysfibrinogenemias are inherited in an autosomal dominant manner, with 1 or more heterozygous mutations affecting fibrinogen release, polymerization, cross-linking, or fibrinolysis. Acquired fibrinogen disorders include acute or chronic liver disease (acute liver failure, cirrhosis), disseminated intravascular coagulation (DIC), use of chemotherapeutic agents such as L-asparaginase, and Kasabach-Merritt syndrome (hemangioma with consumptive coagulopathy). Rarely, autoantibody formation against fibrinogen can develop in association with autoimmune disorders or malignancies.

Clinical presentation

Bleeding can be variable but tends to be most severe in patients with afibrinogenemia and those with Clauss fibrinogen levels <100 mg/dL (see the following section on diagnosis), and includes mucocutaneous, soft tissue, intracranial, perioperative, and recurrent miscarriages. Afibrinogenemia presents most often in infancy with prolonged umbilical stump bleeding. Hemarthrosis is rare. Paradoxically, qualitative fibrinogen disorders have also been associated with a lifetime risk of thrombosis as high as 20% to 30%, though these still constitute an extremely small proportion of venous thromboembolism cases overall.

Diagnosis

Diagnosis is suspected in the setting of both abnormal bleeding and a prolonged PT and aPTT but can also be detected in asymptomatic individuals with these lab abnormalities. Most PT and aPTT assays will be prolonged once fibrinogen levels fall below 100 mg/dL, though this can vary depending on analyzers and reagents used. Corroborating a fibrinogen disorder can be accomplished with a thrombin time and reptilase time, both of which will typically be prolonged. Measuring fibrinogen itself is best performed with the Clauss fibrinogen, a functional assay similar to the thrombin time but using much higher concentrations of thrombin. Immunoassays to

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measure fibrinogen antigen concentration and genotyping of fibrinogen-associated genes are also available to confirm the diagnosis. Dysfibrinogenemias can be challenging to diagnose since the PT, aPTT, and fibrinogen activity and antigen levels can occasionally be within normal ranges; a high degree of clinical suspicion is necessary in these cases.

Treatment

Principles of management are analogous to hemophilia A and B, with both on-demand and prophylactic strategies. For acute bleeding and low fibrinogen levels, the goal is to raise fibrinogen to >100 to 150 mg/dL. This can be accomplished with fibrinogen concentrates, cryoprecipitate, or fresh frozen plasma (FFP). Two plasma-derived fibrinogen concentrates are approved for use in the United States (Fibryga; Octapharma, Lachen, Switzerland, RiaSTAP; CSL Behring, King of Prussia, PA); because of their smaller volume and lower infectious risk, these concentrates are preferred over cryoprecipitate and FFP. The half-life of fibrinogen is anywhere from 2 to 4 days; labs should be repeated often to determine the need for additional dosing to maintain a fibrinogen level of >100 to 150 mg/dL. Bleeding prophylaxis is recommended only in those with a history of severe, life-threatening bleeding and persistently low levels of fibrinogen (<50 mg/dL) and can typically be accomplished with weekly doses of fibrinogen concentrates.

Prothrombin deficiency

Pathophysiology

Both quantitative and qualitative prothrombin defects can be inherited in an autosomal recessive manner, with an overall prevalence of 1 in 2,000,000. A rare, acquired form of prothrombin deficiency is the lupus anticoagulant hypoprothrombinemia syndrome (LA-HPS), caused by an autoantibody to phospholipids with cross-reactivity to prothrombin that accelerates is clearance (but leaves it functionally intact). Other acquired deficiencies of prothrombin can occur in association with chronic liver disease, vitamin K deficiency, and DIC. In these cases, multiple coagulation factors will typically be deficient.

Clinical presentation

Complete prothrombin deficiency is incompatible with life, with no known cases. Bleeding symptoms can include mucocutaneous, intramuscular, and trauma- and surgery-induced. Hemarthrosis may be more common with prothrombin deficiency than in other rare coagulation disorders, as high as 42% in one series. There is a poor correlation between bleeding symptoms and prothrombin levels, though severe manifestations are unlikely unless prothrombin levels are <10% (in individuals with homozygous mutations). Heterozygotes with prothrombin levels >30% may be minimally symptomatic except in the face of significant hemostatic challenge such as major surgery or trauma. Dysprothrombinemias, like dysfibrinogenemias, can have particularly variable presentations, and have also been associated with thromboembolic events.

Diagnosis

The diagnosis of prothrombin deficiency should be considered in the setting of a prolonged PT and aPTT with normal thrombin time and reptilase time. The diagnosis can be confirmed in one of several ways: thrombin activity assay, PT-based one-stage factor activity assay; direct measurement of prothrombin antigen via immunoassay; and prothrombin genotyping. In LA-HPS, PT-based mixing studies will correct, but aPTT-based mixing studies will show persistent prolongation. A dilute Russell viper venom time can be performed in these cases to evaluate for a lupus anticoagulant. The presence of liver failure and vitamin K deficiency should also be evaluated when prothrombin deficiency is suspected.

Treatment

No specific prothrombin-only concentrates exist. Therefore, treatment and prevention of bleeding in patients with prothrombin deficiency is performed with prothrombin complex concentrates (PCC) or FFP. PCC can be either 3- or 4-factor (containing higher amounts of FVII) and can contain factors in their unactivated zymogen form or in activated form (eg, FEIBA). All of these products contain prothrombin and are appropriate treatment options. PCC doses are typically 20 to 40 IU/kg, with a single dose expected to increase the plasma prothrombin concentration by 40% to 60%. Since prothrombin's half-life is 60 hours, doses of PCC can be repeated approximately every 2 to 3 days as needed for treatment of bleeds. Prophylaxis should similarly be limited to individuals with a history of severe bleeding and persistent prothrombin levels <10%, with PCCs dosed once per week. Thrombotic complications with PCC in this population are rare, though caution should be exercised to avoid exceeding recommended doses of PCC particularly in those with qualitative prothrombin defects.

Factor V deficiency

Pathophysiology

Congenital FV deficiency is an autosomal recessive disorder with an estimated prevalence of 1 in 1,000,000 and has been associated with more than 100 different mutations in the *F5* gene. Combined FV and FVIII deficiency

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is an extremely rare condition that results from abnormalities in the FV and FVIII intracellular transport pathway because of mutations in the chaperone proteins, specifically LMAN1 and MCFD2. This autosomal recessive condition typically presents with mild-moderate bleeding symptoms. Finally, acquired FV deficiency has been reported in several scenarios: after exposure to topical bovine thrombin containing trace amounts of FV (topical bovine thrombin has since been largely replaced by human recombinant thrombin); in the Quebec platelet disorder in which excess urokinase-type plasminogen activator causes accelerated proteolysis of FV within platelet granules; and because of autoantibodies to FV in the setting of pregnancy, malignancy, and autoimmune disorders. Liver disease and DIC can also lower FV levels.

Clinical presentation

Similar to other rare factor deficiencies, FV levels show poor correlation with bleeding symptoms. Still, most severe bleeding occurs in those with levels <10%. This inconsistent correlation between lab tests and phenotype may be partially explained by 2 distinct FV storage pools, 1 within the circulation and the other within platelets granules. Bleeding symptoms are often mucocutaneous or provoked by surgery or trauma.

Diagnosis

FV deficiency is diagnosed in those with abnormal bleeding and/or a prolonged PT and aPTT with normal thrombin time and reptilase times. Other common pathway clotting factors (fibrinogen, FII, and FX) will be normal in congenital deficiency, though can be altered in the setting of concurrent disease states (eg, cirrhosis, DIC). FV activity can be confirmed using a PT-based one-stage activity assay. Antigen measurement via immunoassay and genetic testing can also help confirm the diagnosis. FVIII:C should also be measured to differentiate between combined FV/FVIII deficiency and isolated FV deficiency; factor activity levels in the former will often be higher than in isolated FV or FVIII deficiency.

Treatment

Treatment and prophylaxis of bleeding in individuals with FV deficiency is currently limited to FFP and platelet transfusions; PCC and cryoprecipitate do not contain sufficient quantities of FV. A plasma-derived FV concentrate is currently under development. In general, FFP is dosed at 15 to 20 mL/kg and is predicted to raise FV activity by 15%. The half-life of FV following FFP infusion is 24 to 36 hours; repeat dosing should be guided by serial FV activity measurements, the patient's volume status, and ability to tolerate additional FFP. Since platelet α-granules contain 20% of circulating FV in preactivated form, platelet transfusion remains an option if FFP is ineffective, unavailable, or there are concerns about the infusion volume or other adverse effects of FFP. In combined FV and FVIII deficiency, it is critical to additionally provide a source of FVIII via either desmopressin (mild FVIII deficiency) or FVIII CFC (moderate-to-severe deficiency).

Factor VII deficiency

Pathophysiology

FVII deficiency is the most common of the rare factor deficiencies, with an estimated prevalence of 1 in 500,000. It is inherited in an autosomal recessive manner, ascribed to more than 250 unique mutations in the *F7* gene. Acquired FVII deficiency can be caused by liver disease, vitamin K deficiency, or DIC. Accidental or surreptitious ingestion of warfarin or rodenticides should also be considered. Several case series have been reported of patients with a bleeding diathesis related to recreational use of synthetic marijuana products that have been adulterated with "superwarfarins" with extremely long half-lives, requiring months of vitamin K therapy. Finally, acquired anti-FVII autoantibodies have rarely been described.

Clinical presentation

Patients with severe FVII deficiency (FVII <10%) are those most likely to have significant bleeding, ranging from mild epistaxis or menorrhagia to severe intracranial hemorrhage, though some patients in this range have also experienced zero bleeds. Conversely, patients with FVII levels >10% have also been reported to develop severe bleeding. In an international registry, most cases with severe bleeding had levels of 0% to 21%, and those that were asymptomatic had levels of 15% to 35%. Venous thromboembolism has also been reported in up to 4% of patients, indicating that other coagulation pathways remain active despite reduced extrinsic pathway function.

Diagnosis

The laboratory picture of FVII deficiency is that of an isolated prolonged PT with normal aPTT and thrombin time. An isolated prolonged PT should prompt measurement of FVII Early vitamin K deficiency may predominantly affect the FVII activity.

Treatment

Treatment of FVII deficiency is primarily with recombinant FVIIa (NovoSeven). As previously noted, SevenFact

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is a newer rFVIIa product that remains limited to treatment of congenital hemophilia with inhibitors. If rFVIIa is unavailable, 4-factor PCC or FFP can also be used. The recommended dose of rFVIIa for treating and preventing bleeding in congenital FVII deficiency is much lower than for congenital hemophilia, at 15 to 30 μg/kg per dose, with doses repeated every 12 hours as needed. The general goal is to maintain FVII levels >20%, Antifibrinolytics (EACA or TXA) may also be useful for minor bleeding, particularly in those with no or minimal personal history of bleeding. FVII levels of >10% to 20% are typically adequate for surgery. In the setting of severe deficiency and severe or recurrent bleeding, prophylaxis with rFVIIa can be considered, though dosing regimens are largely empiric, most commonly 20 to 40 μg/kg 2 to 3 times weekly. Limited retrospective data demonstrated the efficacy of this regimen despite FVII's known short half-life.

Factor X deficiency

Pathophysiology

Congenital FX deficiency is an autosomal recessive disorder with an estimated worldwide prevalence of 1 in 1,000,000. Acquired FX deficiency can be seen in liver disease and severe vitamin K deficiency. Additional distinct acquired risk factors for FX deficiency are light-chain (AL) amyloidosis and multiple myeloma, in which FX is adsorbed and its activity neutralized by circulating amyloid fibrils or paraproteins, respectively. This has been observed in up to 8% of patients with AL amyloidosis.

Clinical presentation

FX deficiency can be one of the most severe rare factor deficiencies. Interestingly, bleeding phenotype seems to correlate better with FX activity levels than for other rare factor deficiencies and is most severe with levels <10%. Abnormal bleeding in patients with FX deficiency can manifest as mucocutaneous, soft tissue, or gastrointestinal bleeding. ICH has been reported in up to 21% of symptomatic cases.

Diagnosis

Laboratory testing in patients with FX deficiency will show both prolonged PT and aPTT but normal thrombin time, similar to prothrombin and FV deficiencies. FX activity is typically measured using a PT-based one-stage activity assay. Congenital FX deficiency is distinguished from acquired FX deficiency secondary to AL amyloidosis on clinical grounds, though genetic sequencing of the *F10* gene can help. Mixing studies in the setting of AL amyloidosis demonstrate correction and appear consistent with a factor deficiency.

Treatment

A human plasma-derived FX concentrate is available for the treatment and prevention of bleeding in FX deficiency (Coagadex; Bio Products Laboratory, Elstree, United Kingdom), with a typical dose of 25 IU/kg repeated daily as needed for acute bleeds. Other treatment options include PCC and FFP. A typical dose of PCC is 20 to 30 IU/kg and would be expected to increase the plasma FX activity 40% to 60%. Using these agents for bleeding prophylaxis can be considered in severe cases at similar doses once or twice weekly.

In the setting of AL amyloidosis, treatment of the AL amyloid disease itself typically normalizes the FX level. If hemostatic support is needed prior to treatment of the underlying AL amyloidosis, as may occur with bleeding or emergent surgery, similar treatment strategies as described previously may be used.

Factor XI deficiency

Pathophysiology

Congenital FXI deficiency, sometimes referred to as hemophilia C, can be inherited in both autosomal dominant and recessive patterns, depending on the specific *F11* gene mutation. Certain founder mutations have been traced to Ashkenazi Jewish populations, where 1 in 11 are heterozygous and 1 in 450 are homozygous or compound heterozygous. Acquired FXI deficiency can be seen in liver disease and DIC and acquired FXI autoantibodies have been detected in those with malignancies or autoimmune diseases. FXI deficiency leaves intact the extrinsic pathway and FVIII and FIX which are critical for generating the thrombin burst essential for normal hemostasis. This translates to a generally milder bleeding diathesis than some other factor deficiencies.

Clinical presentation

Bleeding in FXI deficiency can be variable, but the majority of affected patients do not sustain spontaneous hemorrhage. Surgical or trauma-induced bleeding is most common, particularly in sites where fibrinolysis is active such as the oral mucosa, gastrointestinal tract, and urinary tract.

Diagnosis

Laboratory testing in the setting of FXI deficiency demonstrates a prolonged aPTT and normal PT and thrombin time. FXI activity is measured using an aPTT-based one-stage activity assay. Antigen measurements and genetic sequencing of *F11* can also be performed.

Treatment

Since the FXI level is such a poor predictor of bleeding, the presence or absence of bleeding with prior traumatic

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events or invasive procedures should be considered when determining bleeding risk and need for treatment. Antifibrinolytic therapy with TXA or EACA should be a mainstay of treatment. For persons with FXI levels <10% or with a personal history of bleeding, replacement of FXI using FFP (15 to 25 mL/kg) can be considered for severe bleeds. To ensure perioperative hemostasis, a combination of antifibrinolytics and FFP are typically used, though rFVIIa has also been successfully deployed. A plasma-derived FXI concentrate is available in some countries, but not in the United States. Alloantibodies against FXI (FXI inhibitor) have been reported to occur following replacement therapy.

Factor XIII deficiency

Overview

FXIII circulates as a heterotetramer consisting of 2 catalytic A subunits and 2 carrier/protective B subunits. FXIII is activated by thrombin and, once activated, covalently cross-links fibrin gamma chains to render a newly formed thrombus more resistant to fibrinolysis.

Pathophysiology

Congenital FXIII deficiency is an autosomal recessive disorder with a worldwide prevalence of 1 in 2,000,000. FXIII deficiency can be caused by mutations in the genes that code for either the catalytic A subunit or the B carrier subunit, though mutations in subunit B are reported to account for <5% of cases of congenital factor XIII deficiency. Acquired FXIII deficiency can occur in the setting of cardiac surgery, malignancy, infection, and inflammatory bowel disease.

Clinical presentation

The clinical phenotype tends to be more severe with A subunit deficiency rather than B subunit. Bleeding symptoms tend to correlate with FXIII levels to a greater degree than other rare factor deficiencies. Patients with FXIII levels <15% are at the greatest risk of spontaneous bleeding. The most common sites of bleeding are umbilical stump, soft tissue, surgical, and ICH. ICH in particular has been reported in up to a third of patients. In addition to bleeding, poor wound healing and pregnancy loss can occur. Heterozygous carriers may still have FXIII activity levels as low as 20% and may display mild bleeding symptoms.

Diagnosis

Laboratory diagnosis requires a high degree of clinical suspicion and measurement of FXIII activity because the results of typical screening tests such as PT, aPTT, and thrombin time are normal. Qualitative assays for FXIII activity (clot solubility) are only abnormal with levels <5%. Quantitative assays are also available and can detect abnormal FXIII levels despite a normal clot solubility test. Genetic sequencing is the most effective means to determine if subunit A or B is affected, important when deciding on specific FXIII replacement therapies for bleeding treatment and prevention (see following section on treatment).

Treatment

Two specific FXIII products are available in the United States for treatment and prevention of bleeding in FXIII deficiency: recombinant FXIII A subunit (Tretten, Novo Nordisk, Bagsværd, Denmark) and human plasma–derived FXIII (Corifact, CSL Behring, King of Prussia, PA). The plasma-derived product contains both A and B subunits and should be used for patients with known B subunit deficiency. Given the relatively high rate of ICH, prophylaxis with FXIII concentrate is recommended in all patients with a FXIII level <10%. Since FXIII has a relatively long half-life of 7 days, hemostatic FXIII levels can be maintained by administering these FXIII concentrates every 4 weeks. If recombinant or plasma-derived FXIII products are unavailable, FFP or cryoprecipitate can also be used, at much lower doses than are required for other indications (eg, FFP 3 to 5 mL/kg).

Vitamin K–dependent coagulation factor deficiency

Overview

Factors II, VII, IX, and X are vitamin K–dependent clotting factors. During synthesis, they undergo γ-glutamyl carboxylation by γ-glutamyl carboxylase and the cofactor vitamin K hydroxyquinone (KH_2). During γ-carboxylation, KH_2 is oxidized to vitamin K 2,3-epoxide, which then undergoes deepoxidation by vitamin K oxide reductase to restore KH_2.

Pathophysiology

Vitamin K–dependent coagulation factor deficiency (VKDCFD) is an autosomal recessive disorder that has been reported to occur in fewer than 30 families worldwide. It is caused by a defect in the γ-glutamyl carboxylase protein or in subunit 1 of vitamin K oxide reductase protein and leads to deficiencies of vitamin K–dependent clotting factors: FII, FVII, FIX, and FX.

Clinical presentation

Clinically, VKDCFD presents at birth with intracranial or umbilical bleeding or early childhood with joint, mucocutaneous, or soft-tissue bleeding.

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Diagnosis

Prothrombin and factors VII, IX, and X are reduced. Distinguishing VKDCFD from acquired vitamin K deficiency requires demonstration of a normal fasting KH_2 concentration.

Treatment

Treatment with oral or parenteral vitamin K1 has been shown to partially or completely restore coagulation factor activities and is the mainstay of long-term therapy for prevention of bleeding. For severe bleeding or refractory to vitamin K1, PCC, or FFP can also be employed.

Gaps in knowledge

Large, well-designed prospective studies of congenital rare factor deficiencies are challenging because of the low disease prevalence. Development of international databases has therefore been critical to establish the natural history and treatment outcomes of these disorders. There is a clear need for consistent data collection and studies on the clinical management of rare factor deficiencies, including in the perioperative setting and with various prophylaxis strategies.

KEY POINTS

- Rare factor deficiencies occur as a result of genetic mutations and acquired disorders.
- Treatment of an associated underlying disorder may lead to the resolution of the acquired deficiency.
- Rare factor deficiencies are distinguished from hemophilia A and B by greater variability in bleeding symptoms and poor correlation with factor activity assays. Bleeding symptoms can range from trauma- or surgery-associated (eg, FXI) to severe spontaneous intracranial bleeding (eg, FX and FXIII).
- Despite high variability, a general rule of thumb is that factor levels <10%-20% tend to correspond to the worst bleeding phenotypes in rare factor deficiencies.
- Few specific factor replacement concentrates are available for patients with rare factor deficiencies.

Disorders of fibrinolysis

Pathophysiology

The fibrinolytic system provides orderly clot remodeling and dissolution. Imbalances in fibrinolysis may lead to excessive fibrinolytic activity through a variety of mechanisms, including increased tPA activity or inadequate inhibition as the result of PAI-1 or α_2AP deficiencies, and may result in excessive bleeding.

Etiology

Hyperfibrinolysis may result from congenital deficiencies of PAI-1 or α_2AP. PAI-1 deficiency is extraordinarily rare, and the genetic alteration causing the disorder has been identified in only a few cases. Defects in α_2AP also have been described. Both conditions are inherited as autosomal recessive traits. Additionally, hyperfibrinolysis may occur because of a variety of acquired conditions, including liver disease and DIC; after surgery, particularly cardiac surgery; and some prostatic diseases and cases of acute promyelocytic leukemia. Although these conditions also contribute to bleeding for other reasons (factor deficiencies resulting from liver disease, consumption of clotting factors in DIC, and platelet dysfunction in cardiac surgery), the possibility of a contributing hyperfibrinolytic state should be considered as specific therapies are available.

Clinical presentation

The clinical presentation of hyperfibrinolysis is highly variable. Hyperfibrinolytic bleeding may occur in isolation as a result of a congenital deficiency; but most commonly, it occurs as a part of a complex coagulopathy in an acquired disorder. Congenital deficiencies of the fibrinolytic pathway may present with delayed bleeding after injury or surgical intervention and may include mucocutaneous or deep-tissue bleeding; however, ICH has been reported in PAI-1 and α_2AP deficiency. Acquired hyperfibrinolysis presents with bleeding at a variety of sites, and in patients with recent surgery, delayed postoperative hemorrhage often occurs at the surgical site.

Diagnosis

Laboratory investigation of the fibrinolytic system is difficult. The euglobulin clot lysis time (ELT) currently is not available in all laboratories, and interpretation of results is not always straightforward. The ELT assesses the capacity of plasma to lyse a clot formed in patient plasma. Under assay conditions, a clot is expected to dissolve within a set period of time, commonly approximately 2 to 6 hours, and a shortened ELT suggests hyperfibrinolysis. Global hemostatic assays are under evaluation for their ability to more accurately detect hyperfibrinolysis. Thromboelastography suggests hyperfibrinolysis by an elevated LY30 (percentage of clot lysed at 30 minutes after assay start).

It is possible to measure a few individual components of the fibrinolytic system, including α_2AP and plasminogen. Although it is possible to measure antigenic levels of PAI-1, the activity assay is problematic because the normal range includes levels of zero, thereby making detection of a dysproteinemic deficiency state impossible. Elevated

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PAI-1 levels have been associated with atherosclerosis and are not associated with bleeding. PAI-1 levels also exhibit diurnal variation, and any one level may not represent either the highest or lowest physiologic level. A deficiency of α_2AP is measurable; however, the correlation of level of deficiency and risk for bleeding is poorly established. It also is possible to measure the fibrinolytic proteins tPA and plasminogen, with a hyperfibrinolytic state expected to result in increased tPA and decreased plasminogen. Again, the correlation between specific levels and the degree of hyperfibrinolysis has not been established.

Therefore, laboratory diagnosis of the fibrinolytic system presently is not optimal, requiring the clinician to rely on clinical suspicion, including the presence of delayed bleeding, the clinical context and, at times, response to therapeutic interventions.

Treatment

The treatment of hyperfibrinolytic bleeding is fairly straightforward except when it occurs as a complex coagulopathy, when treatment requires careful consideration of thrombotic risk. The control of fibrinolytic bleeding is based on the use of antifibrinolytic agents; although several agents are available, 2 are most widely used: EACA and TXA. The mechanism of action of both agents involves competition with negatively charged lysine-rich residues in the kringle domain of plasminogen, which render plasminogen resistant to activation by tPA. Thus, these agents are effective in tissues rich in tPA. Both are available for intravenous and oral administration. Adverse effects and precautions were described previously. When using antifibrinolytic therapy, it is important not to discontinue therapy prematurely because of the risk of delayed bleeding. It is recommended to continue therapy up until the hyperfibrinolysis is felt to have resolved, or possibly on an ongoing basis if a congenital defect is confirmed and ongoing therapy is warranted.

Prognosis and outcomes

Most commonly encountered causes of hyperfibrinolysis are acquired; with trigger resolution, the patient's hemostatic system should return to normal and, provided that catastrophic bleeding has not occurred, patients should recover without sequelae. For the rare patient with a confirmed congenital disorder, management with antifibrinolytic agents, even as prophylaxis, can minimize or reduce bleeding symptoms.

Gaps in knowledge

Accurate diagnosis for disorders of fibrinolysis remains challenging. A reliable, easily performed, reproducible screening assay would represent an important first step in the diagnosis of these disorders, followed by development of specific factor assays for all components of the fibrinolytic system. Levels of deficiency correlated with clinical bleeding could then be better established.

KEY POINTS

- Fibrinolytic disorders are the least well-defined hemorrhagic diatheses.
- Hyperfibrinolytic disorders should be suspected in the setting of delayed bleeding.
- Hyperfibrinolytic disorders are most often acquired, although rare congenital defects have been documented.
- Laboratory diagnosis of fibrinolytic disorders is difficult and inconsistently precise.
- Treatment of hyperfibrinolytic bleeding is based on the use of antifibrinolytic agents, including EACA and TXA.

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